SYNTHESES AND TRANSFORMATIONS OF STRAINED POLYCYCLIC SYSTEMS

A Thesis Submitted
In Partial Fulfilment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

By

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to the

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY, KANPUR

AUGUST, 1979

DEDICATED

TO

MY PARENTS

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Professor Goverdhan Mehta and has been completed under the guidance of Professor M.V. George.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE I

This is to certify that Mr. Bhabatosh Chaudhuri has satisfactorily completed all the courses required for the Ph.D. degree programme. These courses include:

Chm 501	Advanced Organic Chemistry I
Chm 502	Advanced Organic Chemistry II
Chm 511	Physical Organic Chemistry
Chm 521	Chemical Binding
Chm 523	Chemical Thermodynamics
Chm 524	Modern Physical Methods in Chemistry
Chm 541	Advanced Inorganic Chemistry I
Chm 600	Basic Course in Mathematics
Chm 602	Chemistry of Natural Products

Mr. Bhabatosh Chaudhuri was admitted to the candidacy of the Ph.D. degree in August 1976, after he successfully completed the written and oral qualifying examinations.

Head
Department of Chemistry

Convener
Departmental Post-graduate
Committee

CERTIFICATE II

Certified that the work contained in the thesis, entitled: "SYNTHESES AND TRANSFORMATIONS OF STRAINED POLYCYCLIC SYSTEMS" has been carried out by Mr. Bhabatosh Chaudhuri under my supervision and the same has not been submitted elsewhere for a degree.

G. Mehta

Goverdhan Mehta
Thesis Supervisor

Mukherji
for

M.V. George
Co-Guide

ACKNOWLEDGEMENTS

My tenure in the Ph.D. programme under the supervision of Professor Goverdhan Mehta has been highly instructive. It is with deep gratitude that I acknowledge his patient and stimulating guidance.

It will be an ever-cherished memory to have come in close contact with late Professor D. Devaprabhakara. As my co-guide for a semester it was really a blissful experience to feel his perpetual concern for his students.

To acknowledge my indebtedness to Professor M.V. George would perhaps be expressing my temerity. I have always gratefully accepted his benevolence. Often, I have bothered him with mundane trivialities. For those, I owe him my apologies.

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August, 1979. Bhabatosh Chaudhuri

SYNOPSIS

The thesis entitled, "SYNTHESES AND TRANSFORMATIONS OF STRAINED POLYCYCLIC SYSTEMS" is divided into three chapters, 1: Synthetic approaches to trishomocubanes, 2: Novel C_{10}-carbocycles from pentacyclo [5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undecane-8,11-dione *via* Schmidt fragmentation, 3: Revelation of pentacyclo-[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undecane $\rightleftharpoons$ oxa-bird cage equilibrium by ^{13}C NMR spectroscopy and lead tetraacetate fragmentation of some polycyclic systems.

In Chapter 1, various synthetic approaches to the carbocyclic framework, (D_3)-trishomocubane, have been explored as a prelude to a possible synthetic sequence to the dodecahedrane molecule *via* a novel one-step "stabilomer" technique. The various approaches to the trishomocubane system, which were attempted but proved unsuccessful, are initially described. The successful route to various trishomocubanes was developed starting from the readily available pentacyclo [5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]-undecane-8,11-dione. The key step was the smooth and efficient rearrangement of pentacyclo [5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undecane-8,11-diol to 4-mesyloxypentacyclo [6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-7-ol in methanesulphonic acid. The preparation of (D_3)-trishomocubanone from the above pentacyclic diketone in five steps and in high yield has been described. The synthetic sequence did not involve any chromatographic separation or purification step other than crystallization and sublimation. The procedure

involved provides a rapid, simple and versatile entry to various trishomocubane derivatives in multigram quantities. Corollary investigations in the search of the same polycyclic framework led to two unusual but interesting reactions. These have been elaborated at the end. The lactol, 2-hydroxy-2,7-oxa-tetracyclo [6.3.0.$0^{4,11}$.$0^{5,9}$] undecane undergoes a novel phenylation in the presence of a strong acid and the ketol, 11-hydroxypentacyclo [5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undecan-8-one furnishes a novel dimer possessing an oxa-bird cage structure.

In Chapter 2, a rearrangement pathway from pentacyclo-[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undecan-8,10-dione to two new C_{10} carbocyclic systems, tetracyclo [4.3.1.$0^{2,9}$.$0^{4,8}$] decane and 3,7-ethano-tricyclo [3.3.0.$0^{3,7}$] octane, under Schmidt reaction conditions has been delineated. It involves an initial formation of a cyclobutyl carbonium ion and a stereospecific rearrangement to a cyclopropylcarbinyl system. Treatment of pentacyclic dione with sodium azide (1 equivalent) in methanesulphonic acid afforded a mixture of products from which two crystalline compounds were separated. The structure and stereochemistry to these two compounds were assigned on the basis of ^{13}C NMR, 270 MHz ^{1}H NMR, and IR spectral evidence and unambiguously confirmed by single crystal X-ray diffraction work. A few related chemical and photochemical transformations of interest of the two new compounds obtained here are described.

Chapter 3 emphasizes the wide scope of the application of ^{13}C NMR spectroscopy as a looking-glass to mirrorize unequivocally the true structures of certain polycyclic compounds. ^{13}C NMR spectroscopy has been used here to clarify earlier observations and confirm explicable transannular cyclizations in caged-ring compounds. The ^{13}C NMR spectra of several derivatives, particularly the hydrates, derived from pentacyclo-[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undecane-8,11-dione and pentacyclo-[6.4.0.$0^{2,7}$.$0^{3,11}$.$0^{6,10}$] dodecane-9,12-dione have been studied. It has been established that the hydrate derived from the former is an intimate mixture of a monohydrated ketone, and a transannularly cyclized dihydroxy ether bearing an oxa-bird cage skeleton. In a similar manner, ^{13}C NMR spectroscopy showed the existence of an open and an oxa-bird cage form of the ketol, 11-hydroxypentacyclo [5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undecan-8-one derived from the sodium borohydride reduction of the pentacyclic undecane dione. The previously assigned structure to the hydrate from the homologous pentacyclic dodecane dione has been verified. The firm establishment of the structures of the hydrates of the two diones was spurred by the idea that lead tetraacetate fragmentations of the probable dihydroxy ether structures of the hydrates could lead to convenient cyclobutene precursors towards an alternate synthetic strategy to cubyl-caged systems. Hence, lead tetraacetate oxidation of the hydrates were studied. The hydrate of the pentacyclic undecane

dione furnished a novel lactone in high yield via a carbonium ion rearrangement and intramolecular lactonization. The hydrate of the pentacyclic dodecane dione furnished an unsaturated anhydride bearing a tricyclo [4.2.2.$O^{2,5}$] decane framework, and lactone related to the dione. Structures to these products have been assigned on the basis of spectroscopic evidence and plausible mechanism is suggested for their formation.

CONTENTS

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CHAPTER I

SYNTHETIC APPROACHES TO (D_3)-TRISHOMOCUBANES

I.1 ABSTRACT

In this chapter various synthetic approaches to the carbocyclic framework, (D_3)-trishomocubane (50), have been explored as a prelude to a possible synthetic sequence to dodecahedrane (1) via a novel one-step "stabilomer" technique. In this context, the already investigated synthetic routes to dodecahedrane (1) have been briefly reviewed. To begin with, various approaches to the trishomocubane system, which were attempted but proved unsuccessful, are described. The successful route to various trishomocubanes was developed starting from the readily available dione (56) and is schematically presented in Scheme I.16. The key step was the smooth and efficient rearrangement of the endo, endo-diol (100) to the hydroxy-mesylate (101). Jones oxidation of 101 gave the keto-mesylate (104). Wolff-Kischner reduction, using Huang-Minlon

modification, of 104 yielded trishomocubanol (105). Lithium aluminium hydride reduction of hydroxy-mesylate (101) furnished the diol (103), which could be oxidized to the dione (64) with Jones reagent. The procedure makes available trishomocubanone (51) and the dione (64) in multigram quantities without involving any chromatographic separation or purification step other than crystallization and sublimation. Finally, some interesting reactions of ketol (92) and lactol (107) which were unexpectedly encountered, have been discussed. The lactol (107) undergoes a novel phenylation to 111 in the presence of a strong acid, whereas the ketol (92) furnishes a novel dimer possessing an oxa-bird cage structure (118).

I.2 INTRODUCTION

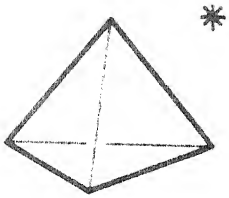
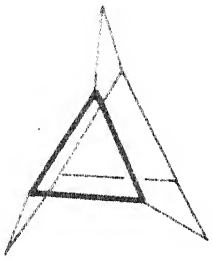
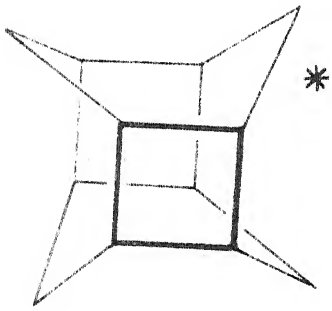
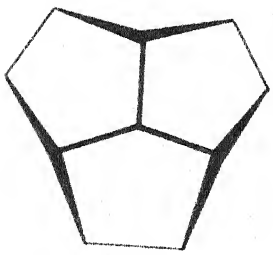
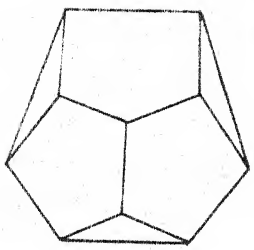
The chemistry of bridged polycyclic systems is an area of intense activity and sustained fascination in organic chemistry. Keen interest in the carbocyclic systems emanates from a variety of considerations. For example, many carbocyclic systems possess interesting shapes and symmetries reminiscent of familiar objects in daily life and constitute an enticing arena for the creativity of synthetic organic chemists. Some of these bridged cyclic systems are also strained, and highly prone to a variety of carbonium ion, thermal and photochemical rearrangements.[1-8] These rearrangements have often provided mechanistic clues to many intriguing reactions, served as probes for investigating "structure-

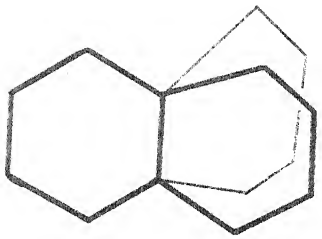
activity" relationships[9] and helped to complement, contradict, or confirm the existing theoretical predictions.

Among the bridged polycyclics, those molecules whose architecture are endowed with enchanting symmetries are of particular interest. In fact, from time immemorial symmetry has fascinated man. Since the times of Pythagoras and Plato symmetry seems to have overawed him. Its manifestations have been revealed in profundity in the beauteous architectural expositions throughout the growth of civilization, from the immaculate Gothic steeples to the marvellous dome of the Sistine Chapel.[10] It seems as an obvious corollary that the modern scientific mind has imbued the tenets of the past and has seeked the elements of symmetry at the molecular level in the spheres of his endeavour.[11] Hence, it is not a great surprise that molecular shape, form, and symmetry have played a great role in organic chemistry.

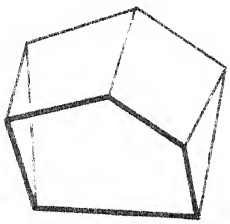
If one recounts, one would observe that a few elements of symmetry were known very early in the history of chemistry. Tartaric acid, for instance, having an axis of symmetry, was extensively studied by Pasteur.[12] However, the notions of symmetry acquired aesthetic beauty[13] with the advent of polycyclic systems. A number of carbocyclic compounds with different elements of symmetry have been synthesized or hypothesized. Structures of some of these compounds with varying complexities, from tetrahedrane to dodecahedrane, are enumerated in Scheme I.1.

Scheme I.1

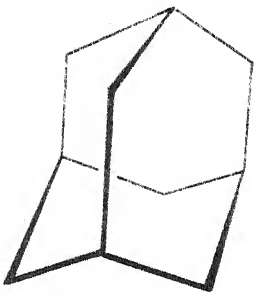
Structure	Name (symmetry)	Reference
	Tetrahedrane (T_d)	14
	Triasterane	15
	Tetrasterane	16
	Perhydrotriquinacene	17
	Diademane	18



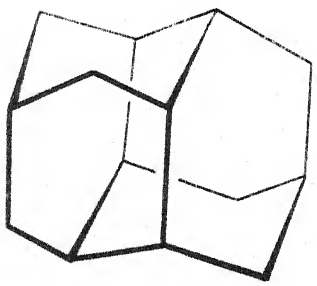
* [4 4 4] Propellane (D_3) 19



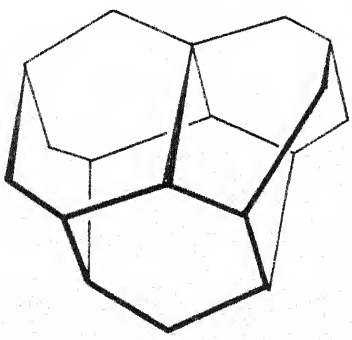
* Cuneane 20



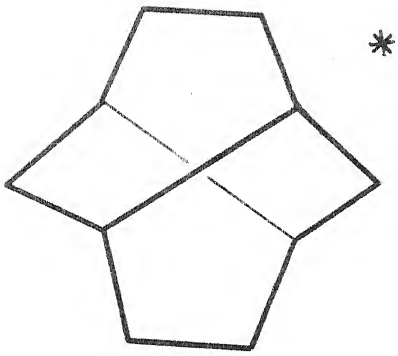
* Adamantane (T_d) 21



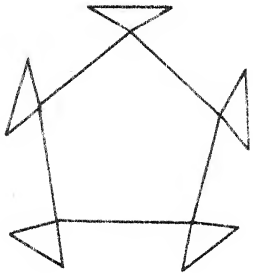
* Congressane (Diamantane) 22



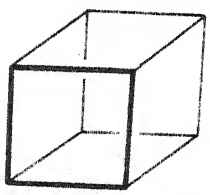
* Triamantane 23



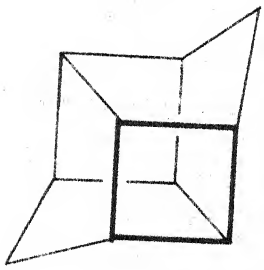
* Twistane (D_2) 24



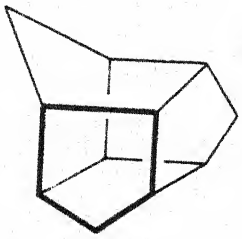
* [5] Rotane 25



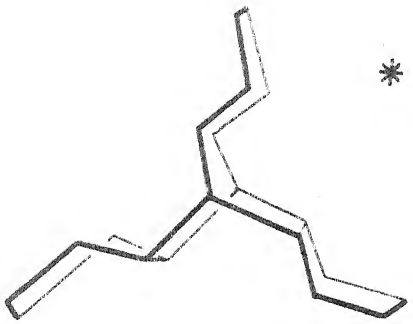
* Cubane (O_h) 26



* Bishomocubane 27

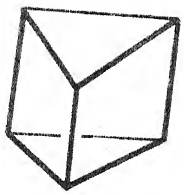


* Trishomocubane (D_3) 28,29



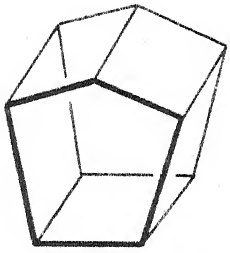
*

Perhydrotripticene (C_{3h}) 30

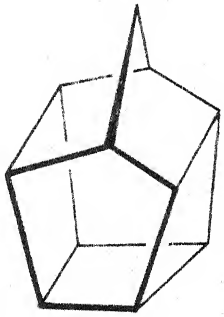


*

Prismane 31

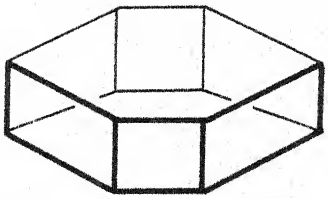


Pentaprismane 32

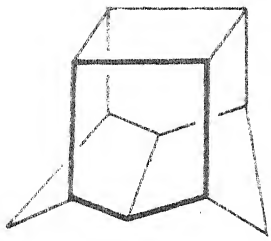


*

Homopentaprismane 28 , 33

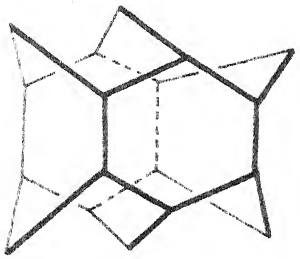


Hexaprismane 34

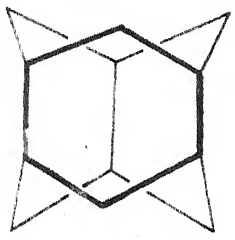


*

Bishomopentaprismane 35
(Bird-cage compound)

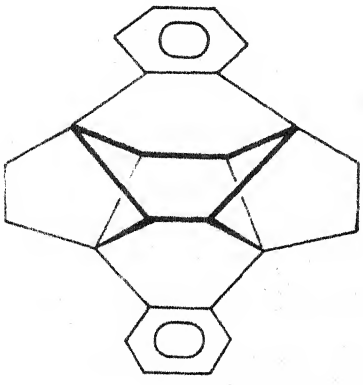


[6] Peristylane 36
(Hexaasterane)



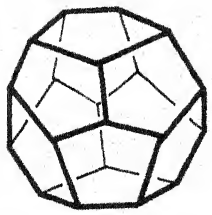
*

Iceane (D_{3h}) 37



*

Dibenzoequicene 38



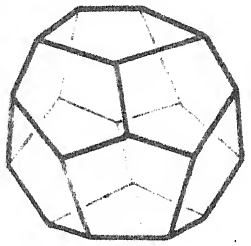
Dodecahedrane (I_h) 39

Many of them are strained, others strain-free. The listing of the various systems is only illustrative and not exhaustive. Among the molecules listed in Scheme I.1, those whose parent hydrocarbons have been synthesized are superscribed with a single star. Those molecules whose derivatives, only, have been made are marked with a double star. Unmarked ones have not yet been prepared.

Amongst the molecules listed in Scheme I.1, the dodecahedrane, $(CH)_{20}$ molecule, is one which has attracted widespread attention[40-52] and has the highest known elements of symmetry (I_h). From the time of the ancient mathematicians, the five perfect geometric solids, the tetrahedron, the cube, the octahedron, the icosohedron and the dodecahedron have been sources of variegated fascination. The interest in dodecahedron, for organic chemists, has been more intense due to the fact that it is endowed with a most remarkable topology. It embodies twelve five-membered rings fused in a relatively strain-free array. The completely enclosed cavity of the structure does not have any solvation capability. The dodecahedrane molecule has been pictured as divided into ethanoid hydrocarbon fragments, all of them being equivalent, rigid, practically angle strain-free though perfectly eclipsed.[40]

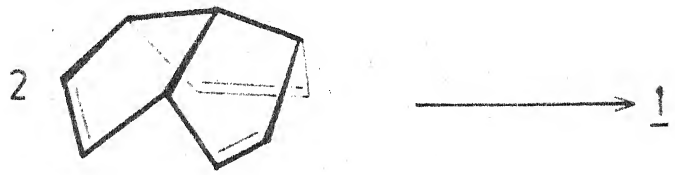
Several approaches to dodecahedrane (1) have been investigated. All of them envisage tactical and step by step acquisition

of fused cyclopentanoid precursors.



1

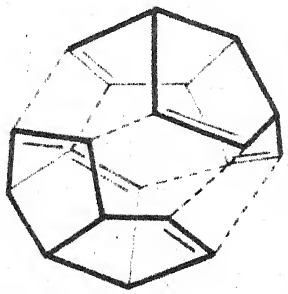
One particular approach that held early promise was the dimerization[41] of triquinacene (2).



2

2 → 1

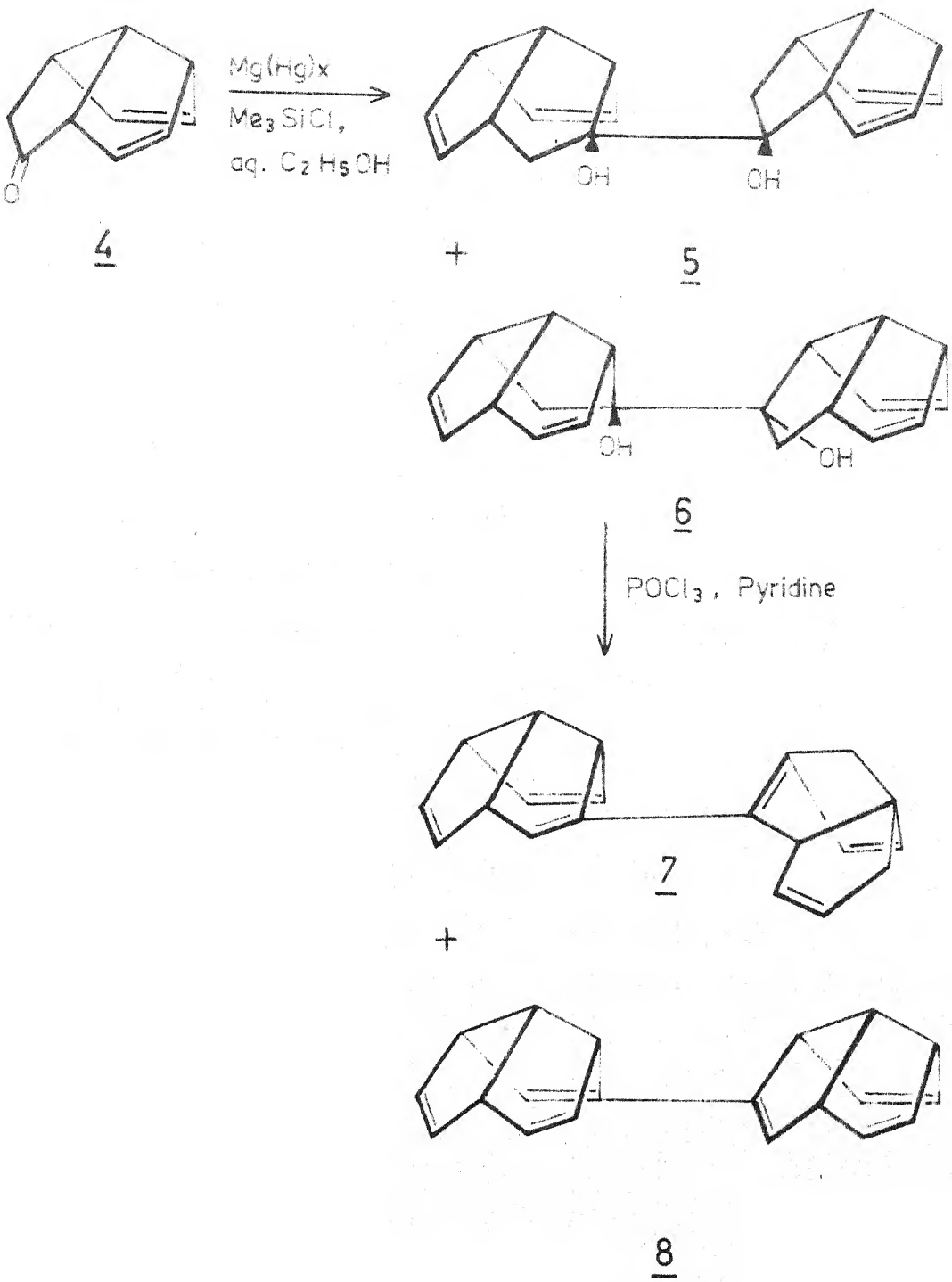
It was anticipated that the two $C_{10}H_{10}$ halves when properly oriented (3) could be coaxed into six-fold carbon-carbon bond formation.



3

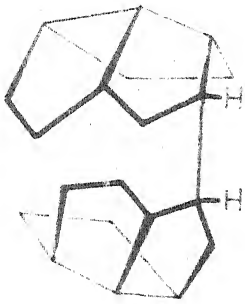
These efforts have so far proved abortive. However, a few dimeric dl (7) and meso-bistriquinacenes (8)[42,43] (Scheme I.2) as well as diastereoisomeric bivalvanes (9 and 10)[42,43] have been

Scheme I.2

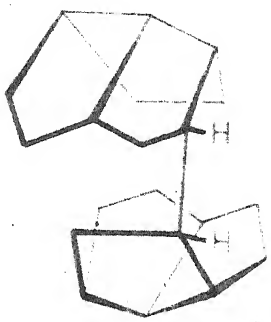


4 + 5 + 6 + 7 + 8

reported which have refused to cyclize any further.



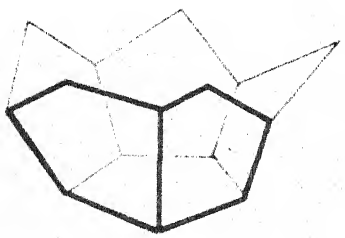
9



10

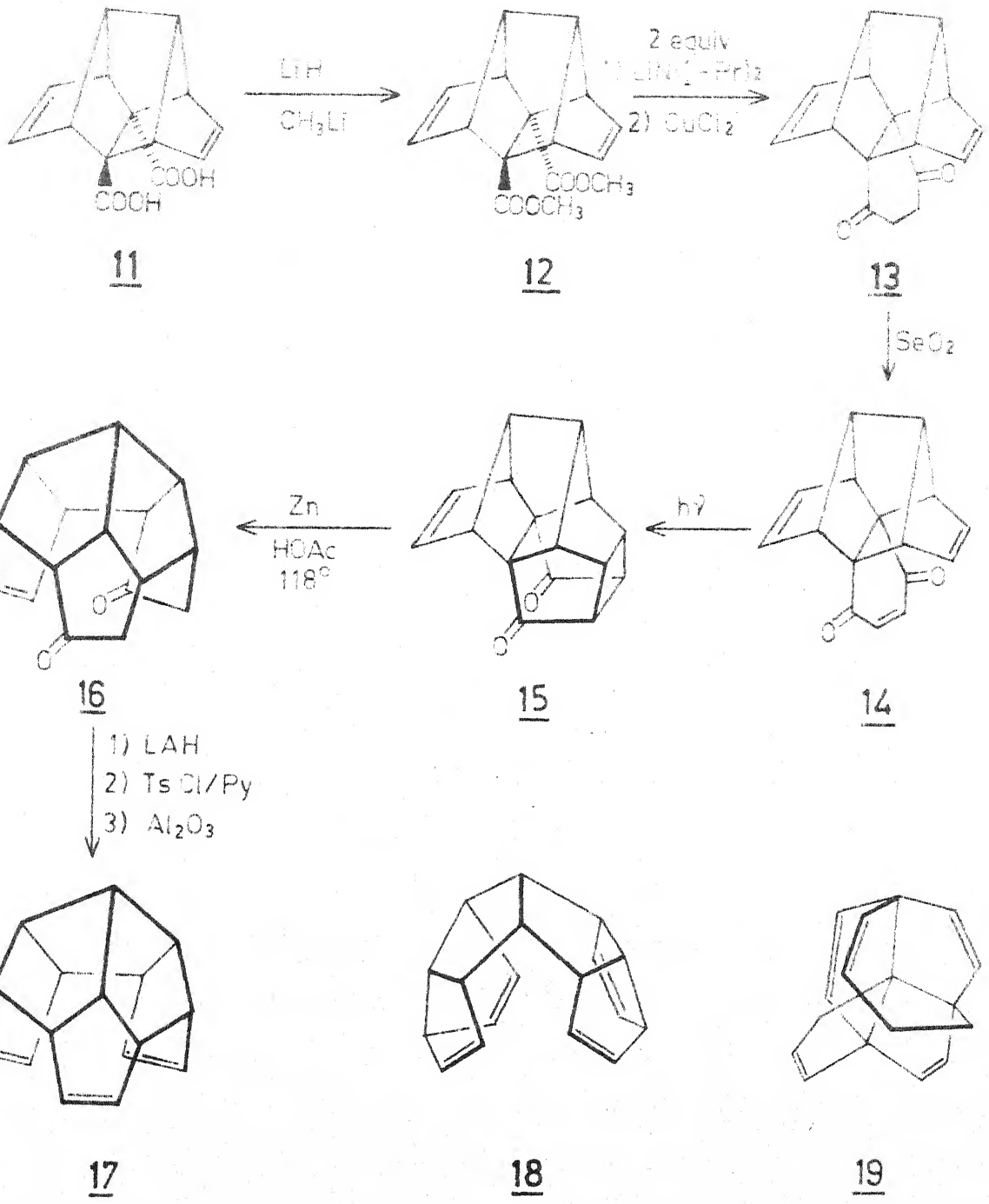
Paquette has also conceived a related approach *via* fused triquinacenes. His route involves hexaquinacene. The C_{16}-hexaquinacene (17), as distinguished from other hexaquinacenes having eighteen (18) and seventeen (19) constituent carbon atoms, possesses a highly convex topology with three mirror-symmetry planes intersecting a three-fold rotation axis. Paquette has recently reported[44] a synthesis of hexaquinacene in the search of the dodecahedrane molecule (Scheme I.3).

Eaton has considered the dodecahedrane problem from another perspective and has pinned his faith on a novel and aesthetically pleasing "bowl" and "lid" approach. His synthesis of the "bowl" with fluted rim, appropriately termed peristylane (20)[45]



20

Scheme I.3



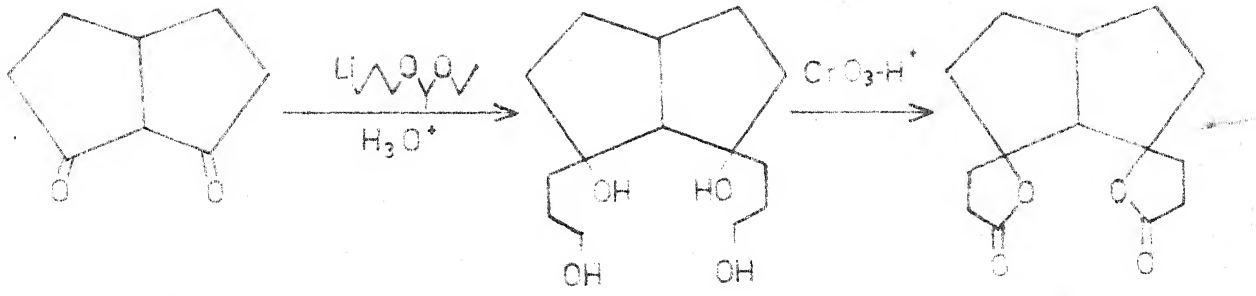
11 12 13 14 15 16 17 18 19

represents a simple and elegant way of building a network of six five-membered rings which accounts for the fifteen of the twenty carbon atoms present in dodecahedrane (1). Dodecahedrane formation from 20 would involve putting a cyclopentanoid "lid" on a suitably functionalized peristylane frame. Eaton has reported a synthesis of functionalized peristylane (29)[46] (Scheme I.4).

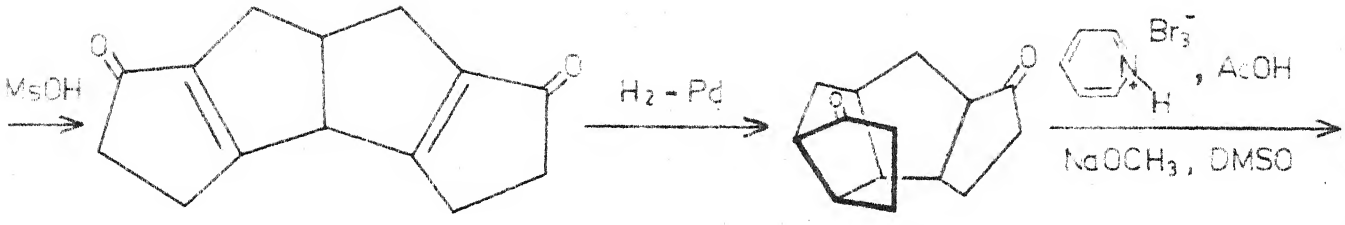
Finally, Paquette has ingeniously coupled his "Domino Diels-Alder" approach[42,47-50] with Eaton's strategy to synthesize a trisecododecahedrane derivative (42) as detailed in Scheme I.5. This is the closest organic chemists have reached to their most prized and sought after molecule.

The accomplishment of the dodecahedrane molecule by stepwise synthetic routes still appears considerably away. Evidences of the strenuous and, so far, futile efforts of several workers can be gauged by a glimpse at the schemes entailed, involving pathways to probable precursors to dodecahedrane (1). In view of the limited success of the stepwise routes to 1, an entirely different and conceptually novel approach to dodecahedrane (1) could be *via* thermodynamically controlled polycyclic isomerization of suitable precursors. This technique is the "stabilomer approach" pioneered by Schleyer,[53] McKervey[54] and others. It involves a one-step, Lewis acid-catalysed isomerization to the most stable isomer (the "stabilomer"). The term "stabilomer", based on the German "stabil" is defined as that isomer possessing

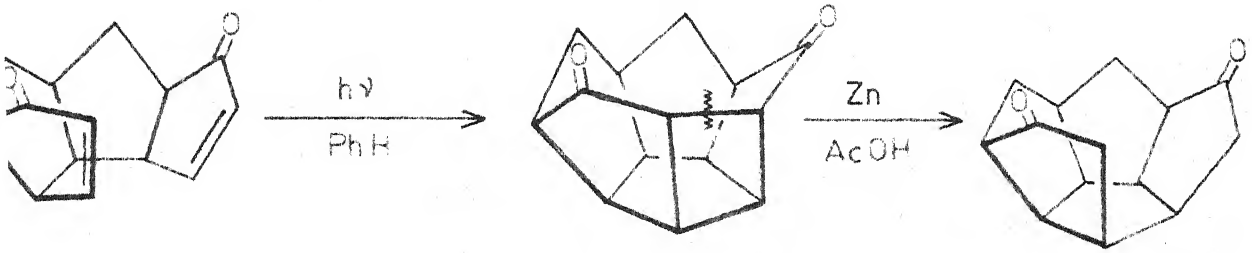
Scheme I.4



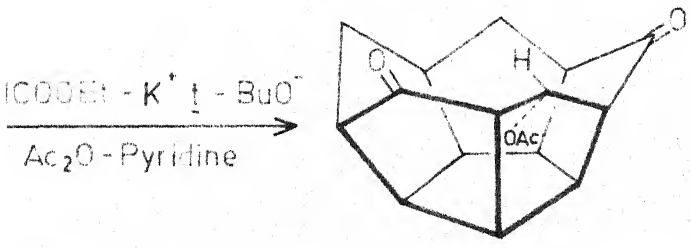
21 22 23



24 25

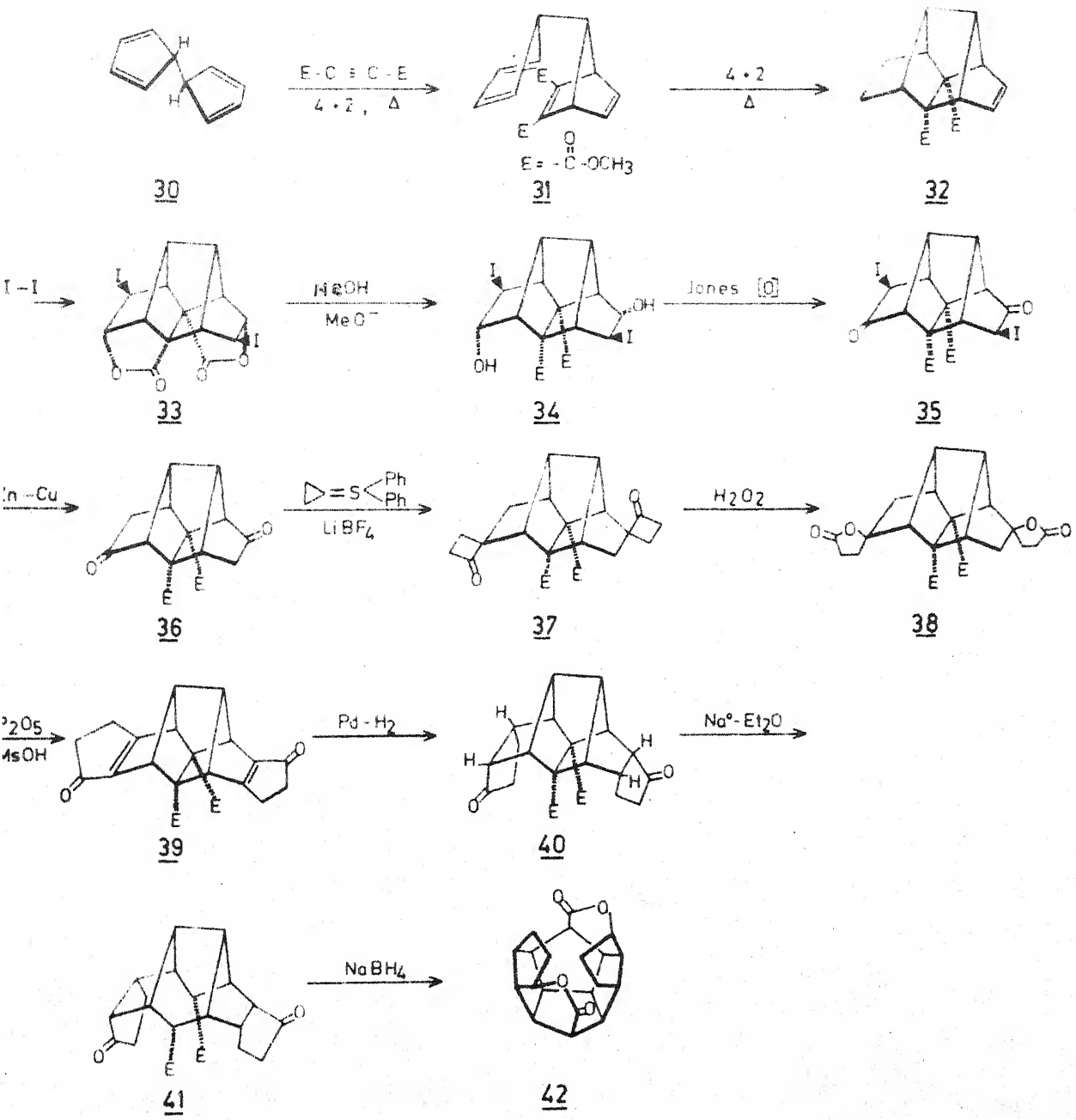


26 27 28



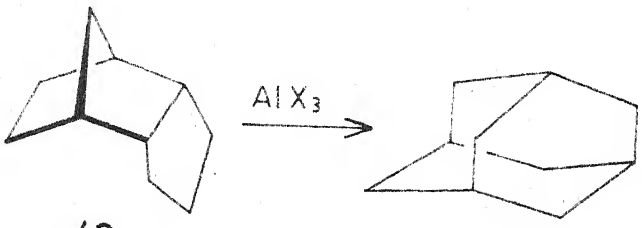
29

Scheme I.5


E-C ≡ C-E
4 + 2 , Δ
E = -C-OCH3
4 + 2
Δ
I – I
MeOH
MeO⁻
Jones [O]
Zn – Cu
LiBF4
H2O2
P2O5
MsOH
Pd - H2
Na° - Et2O
NaBH4
30
31
32
33
34
35
36
37
38
39
40
41
42

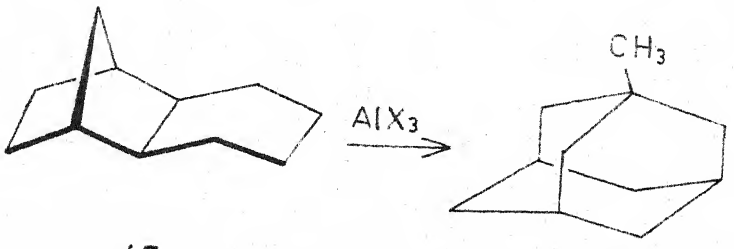
the lowest free energy of formation at 25°C in the gas phase.[55] If successful, this process would be short as well as economical.

The above approach has already found extensive and useful applications in the synthesis of adamantane and higher adamantalogues, congeners of the "Diamond family".[21,23,56-58] The acid-catalysed isomerization of tetrahydrodicyclopentadiene (43), a tricyclic $C_{10}H_{16}$ hydrocarbon, into the thermodynamically more stable diamond lattice structure of adamantane (44), was one of the first examples of this type of rearrangement.[21,56]



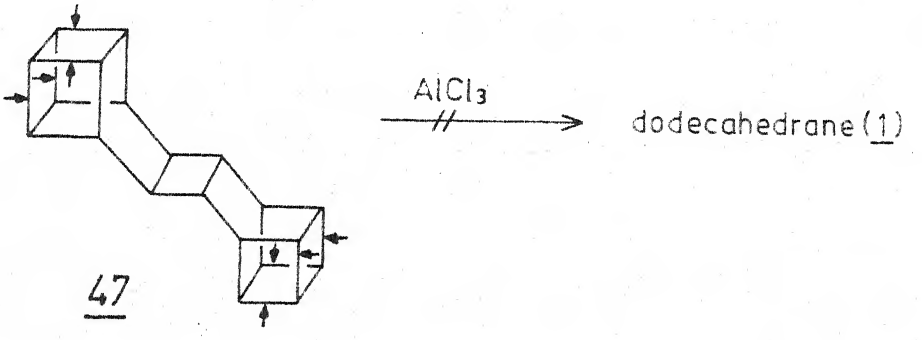
43 44

When the higher homologue, tetramethylenebicyclo[2.2.1]heptane (45), a tricyclic $C_{11}H_{18}$ hydrocarbon was used as the precursor, the isomeric stabilomer 1-methyl-adamantane (46) was obtained.[59]

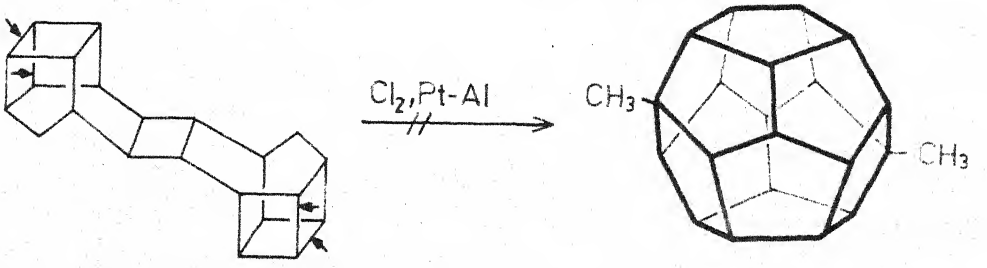


45 46

It would follow from these examples that a polycyclic precursor having twenty to twenty-two carbon atoms with ten or twelve cyclopentanoid rings, and bearing a globular shape could serve as a precursor to dodecahedrane or its methyl-substituted derivatives. One of the early efforts along these lines was by LeGoff,[60] who unsuccessfully tried to isomerize the basketene photodimer (47, $C_{20}H_{20}$) to dodecahedrane (1) with $AlCl_3$. A similar route utilizing the photodimer of homobasketene (48) gave exclusively disproportionation products, containing lesser number of rings than 48, upon treatment with $AlBr_3$. Even the use of McKervey catalyst[61,62] (chlorinated Pt-Al), known to give less disproportionation than AlX_3, proved futile giving no dimethyldodecahedrane (49).[63]



47

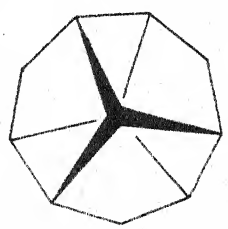


48 49

In both the cases, disproportionation rather than isomerization proved to be the major pathway, which could be ascribed to the presence of strained bicyclo[2.2.0]hexane unit present in 47 and 48. The strained cyclobutane bonds (as marked with arrows) are detrimental to isomerization as they tend to open up, preferentially. Therefore, a polycyclic network devoid of such structural moieties could be the suitable precursor for isomerization to dodecahedrane system.

One such carbocyclic framework is trishomocubane (50),[28,29] a $C_{11}H_{14}$ strain-free homocubane derivative, entirely composed of five-membered rings. It is a $C_{11}H_{14}$ stabilomer, thermodynamically the stablest of all the possible isomers. This has been predicted by empirical force-field calculations. The calculated heats of formation and the strain energies happen to be the lowest of all possible isomers, as found by Engler[64] and Allinger.[65] The values are given in Table I.1 These findings have been corroborated by experimental studies.[66]

TABLE I.1

	$\Delta H^{\circ}f$, Kcal/mol.		Strain Energy, Kcal/mol.	
	Engler	Allinger	Engler	Allinger
 50	9.38	11.32	42.05	44.13

Dimeric structures,* 52 and 53, containing twenty-two carbon atoms, derived from trishomocubanone (51) could serve as precursors for dodecahedrane (1) and give either 49 or the seco-derivative (54), as shown in Scheme I.6. Recent, force-field calculations have indicated that the non-methyl, bishomododeca-hedrane (55) is 18 kcal/mole less stable than dimethyl-dodeca-hedrane (49).[70] A possible acid-catalysed 1,2-shift product from 52, the spiro (53), will probably give dimethyl-seco-dodecahedrane (54).

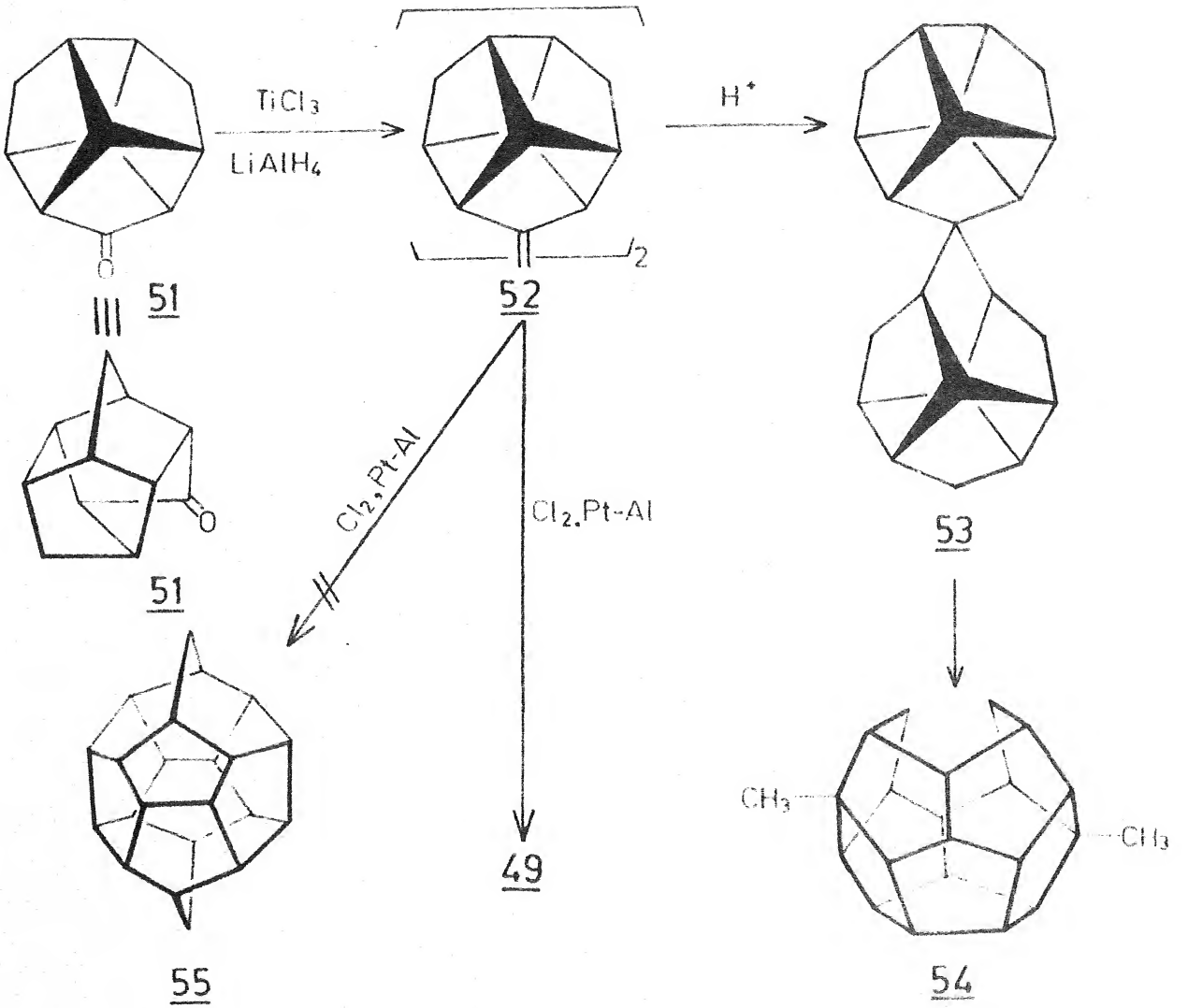
Thus, with a long range and somewhat distant objective of dodecahedrane at the back of our mind, we became interested in the synthesis of trishomocubane ring system. This system, in its own right is a remarkably novel system. Its (D_3) symmetry is very rare[66,71] and, indeed, till now remains one of the few rigid (D_3) organic molecules that are available. Moreover, the functionalized trishomocubane derivatives could serve as pre-cursors of some interesting and not easy to synthesize carbo-cyclic systems through bond breaking processes indicated in Scheme I.8.

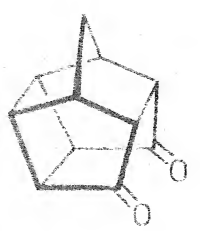
With some of the objectives enumerated above, we started a programme in 1974-75 towards an efficient synthesis of

---

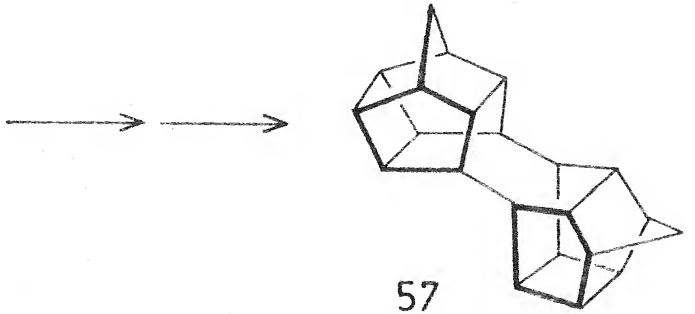
*Many other dimeric structures, e.g., 57, 60 could be considered, Scheme I.7. 57 has correct composition for 49. If the ketone of the norbornadiene cage dimer (58) can be prepared, it can be condensed[67-69] with 59 to give 60. Polycycle 60 on hydrogenation and further rearrangement should give tetramethyl-dodecahedrane (61).

Scheme I.6



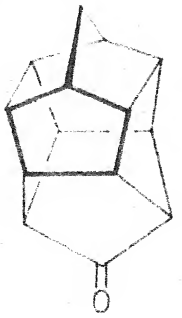


56

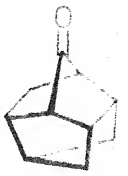


57

49

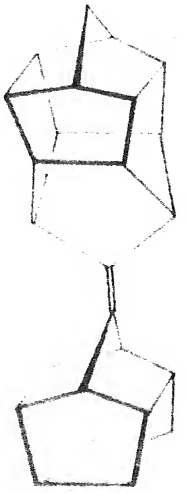


58



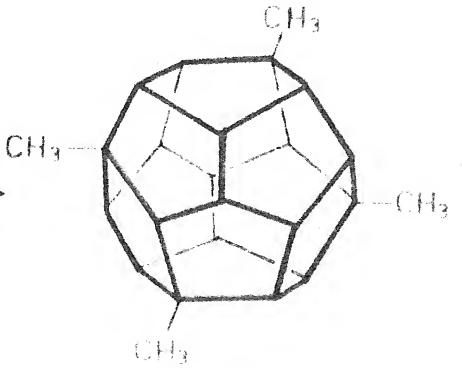
59

, $TiCl_3$, $LiAlH_4$



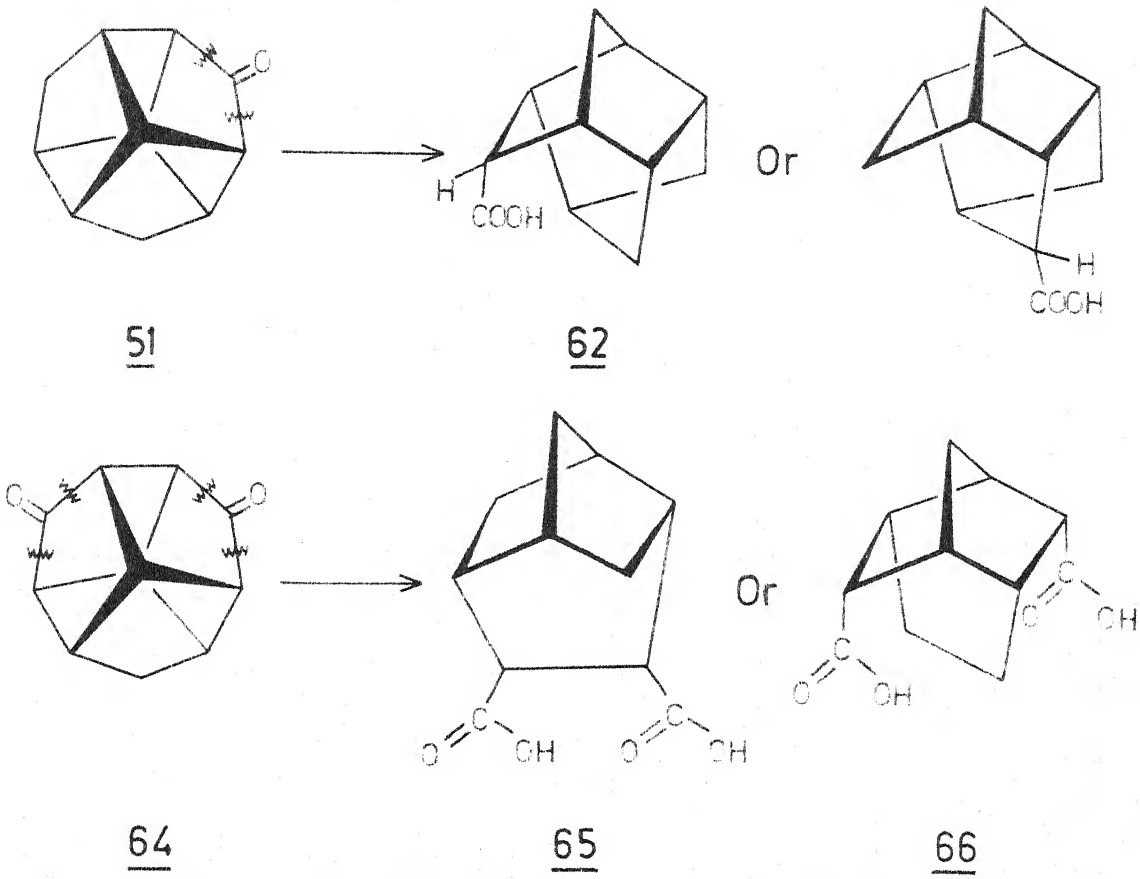
60

1. H_2
2. Cl_2, Pt-Al



61

Scheme I. 8

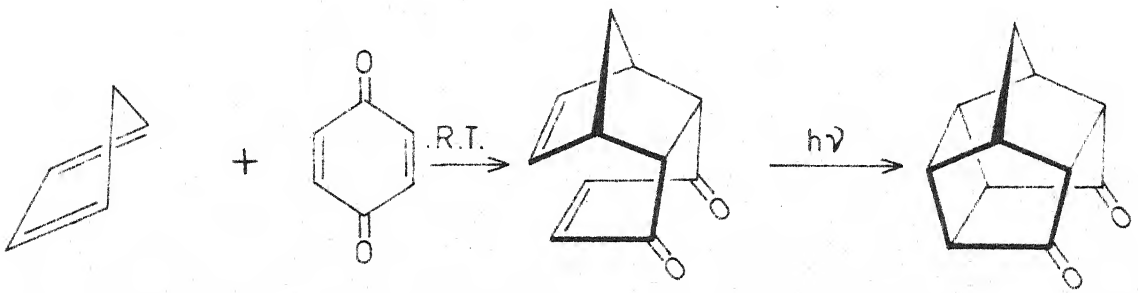


51 62

64 65 66

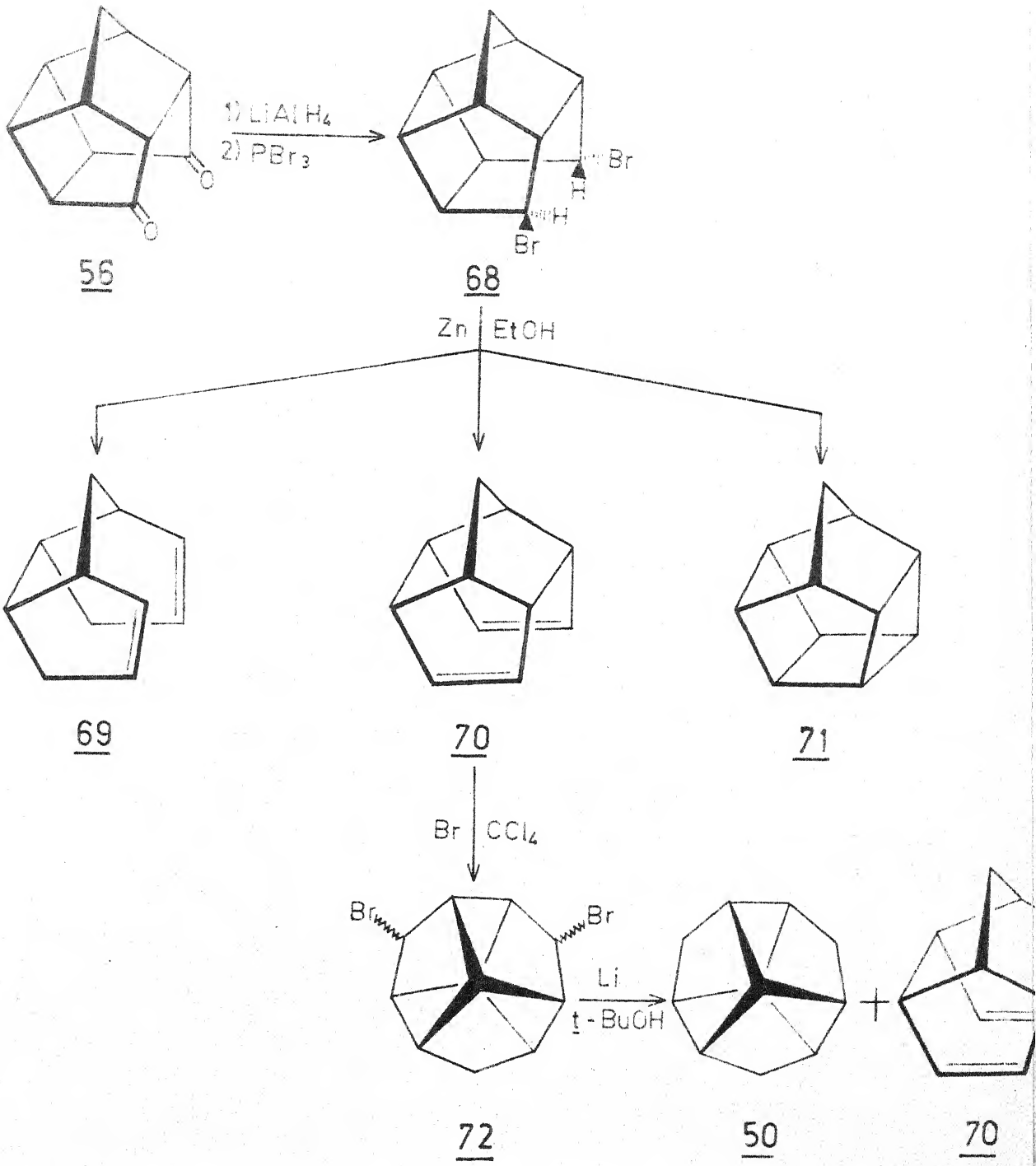
functionalized trishomocubanes. At the time of initiation of our project, only one report of entry into the trishomocubane system had been described in the literature. It was by Underwood and Ramamoorthy.[28] Their preparation of the parent trishomocubane is summarized in Scheme I.9. However, during the past three years there has been unprecedented interest in the preparation of trishomocubane derivatives. Several groups round the world have reported the syntheses of this ring system along almost similar lines.[28,29,66,72-78] Quite remarkably, the pentacyclic dione (56)[79] readily available from the photolysis of cyclopentadiene and p-benzoquinone Diels-Alder adduct (73)[80] has served as the ubiquitous starting material for all these approaches (Scheme I.10).

Scheme I.10



73 56

Scheme I.9



56 68 69 70 71 72 50 70

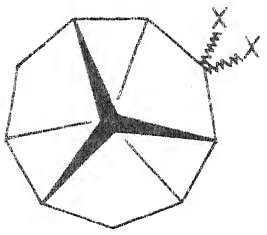
Our own successful synthesis of the trishomocubanes, delineated here, makes use of the pentacyclic dione (56) and was achieved through many trials and failures. Some of these trials may now look somewhat trivial, particularly in the light of many successful syntheses that have been recently achieved.[66,72-74] However, much time and effort was expended in these endeavours and, therefore, a brief description of these in the results section, along with our own successful route must be viewed in that perspective.

In this chapter of the thesis, we first describe the various approaches to the trishomocubane systems, then the successful route to trishomocubanone (51), trishomocubane dione (64) and several other derivatives, and finally some unexpected but interesting reactions of the polycyclic systems 92 and 107. The synthetic sequence to the various derivatives of trishomocubane developed independently by us, although not original in conception, is short, convenient and versatile.

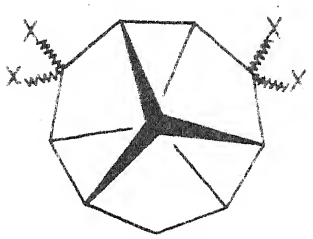
I.3 RESULTS AND DISCUSSION

As stated above, the readily available pentacyclic dione (56)[79] appears to be ideally suited as starting material which has sufficient functionality and proper disposition for

elaboration into mono- and bi-functional trishomocubane derivatives 74 and 75.



74

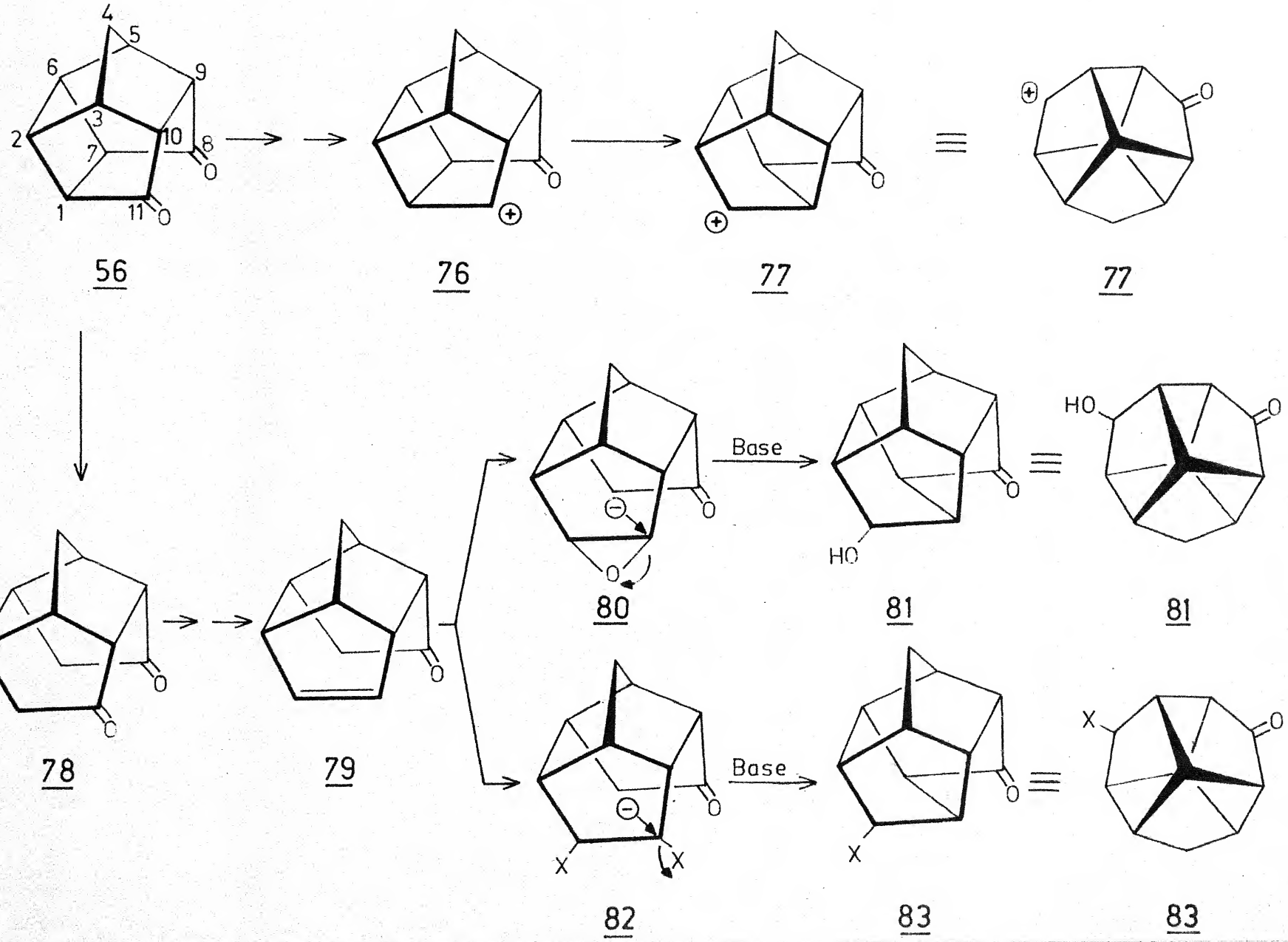


75

Conceptually, the dione (56) could be transformed into substituted trishomocubanes via two simple and straightforward routes, Scheme I.11.

The first one would involve the creation of an electron-deficient carbon at C_{11} and the rearrangement of the cyclobutylcarbinyl carbonium ion (76) to the more stable cyclopentyl carbonium ion (77), bearing the framework of trishomocubanes. The second pathway could be visualized as the cleavage of the dione (56) to the dione (78), and elaboration to the enone (79). Functionalization of the double bond as in 80 and 82 followed by intramolecular alkylation could provide an entry to the trishomocubane system.

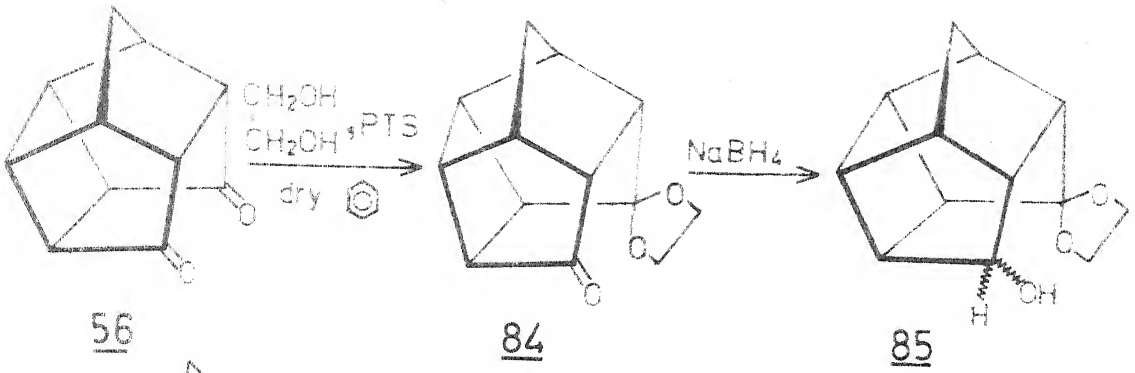
Initially, we thought of only subtle alterations in the already chalked out carbonium ion rearrangement pathways delineated by another group.[28] The reaction sequence pursued is depicted in Scheme I.12. The readily available diketone (56) (Scheme I.10) underwent selective ketalization[33] with



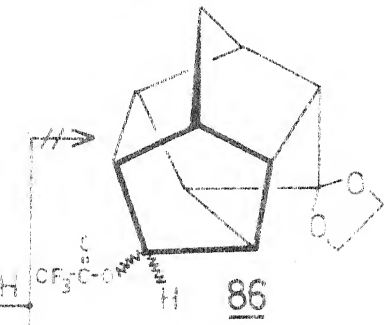
56 76 77 77

78 79 80 81 81

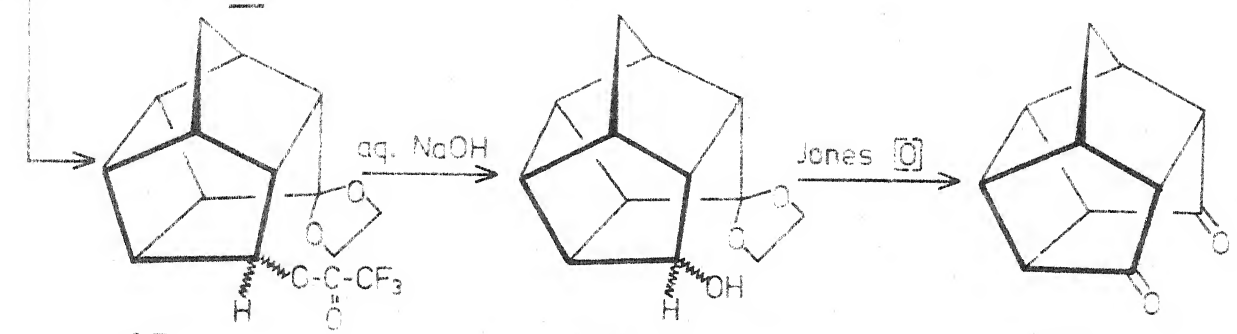
82 83 83



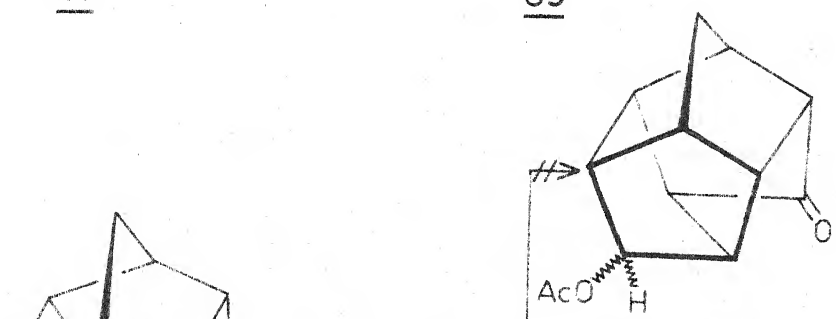
56 84 85



86



87 85 56



88 85 89 56

ethylene glycol and a few crystals of p-toluenesulphonic acid to give the monoketal (84), m.p. 73-74°C (IR, ν_{max}: 1750, carbonyl and 1105 cm^{-1}, ketal). The monoketal (84) was reduced with sodium borohydride to give the hydroxy-ketal (85) as a syrupy liquid (IR, ν_{max}: 3600, hydroxyl, and 1130 cm^{-1}, ketal). The hydroxy-ketal (85) in methylene chloride solution was stirred with trifluoroacetic acid (TFA), known for its ability to induce facile carbonium ion rearrangements, in an effort to get 86. The product obtained was a trifluoroacetate, (IR, ν_{max}: 1770, 1745 cm^{-1}, trifluoroacetate), which had the ketal functionality intact. In order to establish whether the contemplated rearrangement had at all occurred, the trifluoroacetate was hydrolysed with aqueous sodium hydroxide and the resulting hydroxyl compound was oxidized with Jones reagent.[81] The oxidation product, to our disappointment, was found identical (superimposable IR spectrum) with the starting dione (56). This established beyond any doubt that no rearrangement had occurred and it was 87 not 86 which was formed during the TFA rearrangement. Similarly, attempted rearrangement of hydroxy-ketal (85) with boron trifluoride-acetic acid - acetic anhydride mixture yielded only the unrearranged acetate (89), instead of the acetate (88) of the trishomocubane system. Hydrolysis of the acetate and Jones oxidation,[81] once again, led to the starting dione (56).

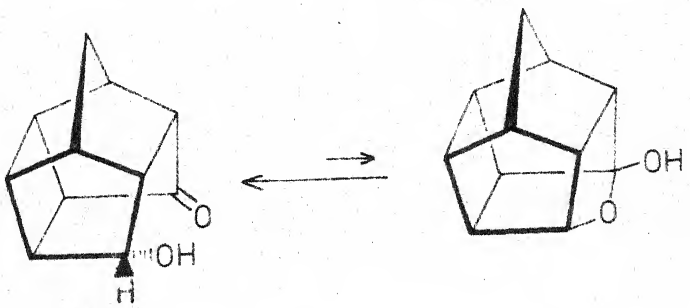
At this stage, we thought that introduction of a good leaving group at C_{11} would promote the expected rearrangement.

Also, it was contemplated that with the presence of a leaving group at C_{11}, the compound might be more amenable to the rearrangement, and reductive elimination could be carried out to give a monofunctional derivative (91). Of course, we were aware of the fact that in this case the geometrical disposition of the leaving and migrating group was not favourable for a concerted rearrangement.

The hydroxy-ketal (85) on reaction with methanesulphonyl chloride in pyridine furnished the crystalline mesylate (90), m.p. 128-129°C (IR , ν_{max}: 1345 and 1175 cm^{-1}, mesyloxy). The mesylate (90) proved unusually resistant to solvolysis, perhaps due to the steric hindrance of the ketal group. (Both the mesyloxy and the ketal oxygen at C_8 and C_{11} are endo and, therefore, directed inside the molecular cavity.) Similarly, reduction of the ketal-mesylate (90) with lithium aluminium hydride led to the formation of the hydroxy-ketal (85) rather than the reductive elimination product (91)(Scheme I.13).

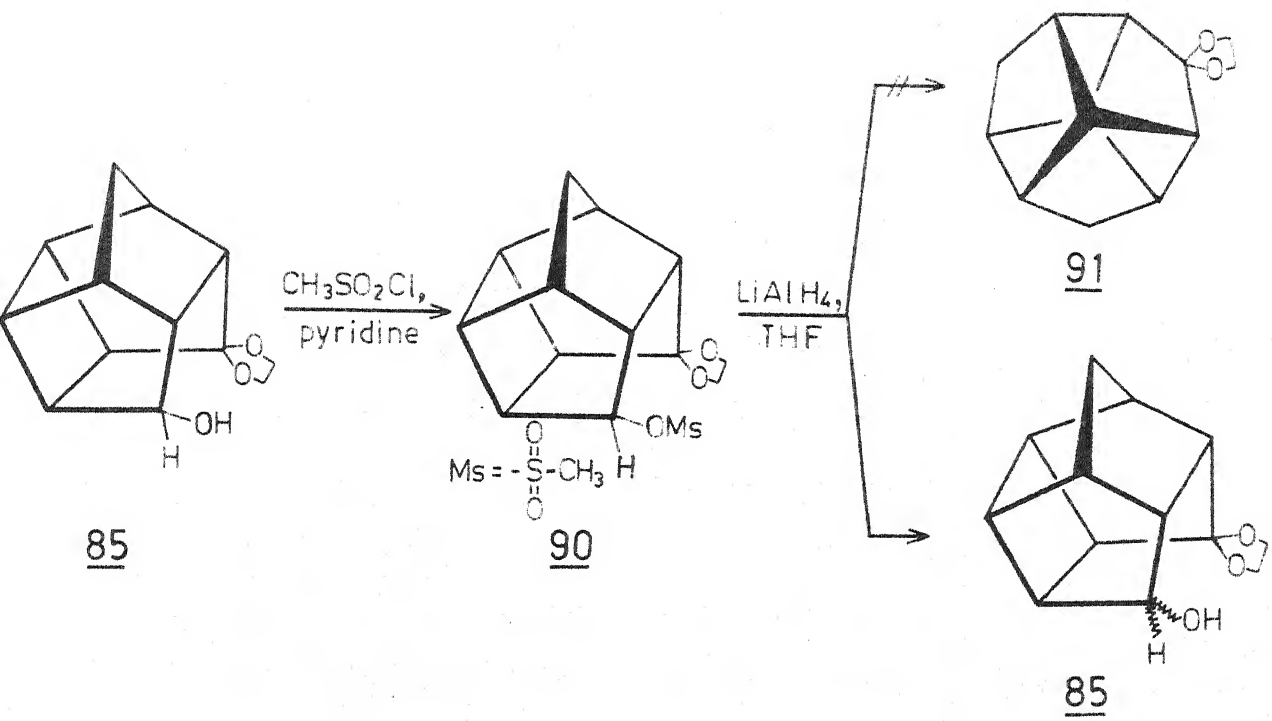
It was, therefore, decided to employ the keto-mesylate (94) in place of 90 . Controlled sodium borohydride reduction of the dione (56) furnished the hydroxy-ketone (92) in 68% yield*.

*We have discovered that the hydroxy-ketone is in equilibrium with its oxa-bird cage form as shown below. These results are discussed in detail in the last chapter of the thesis.



92

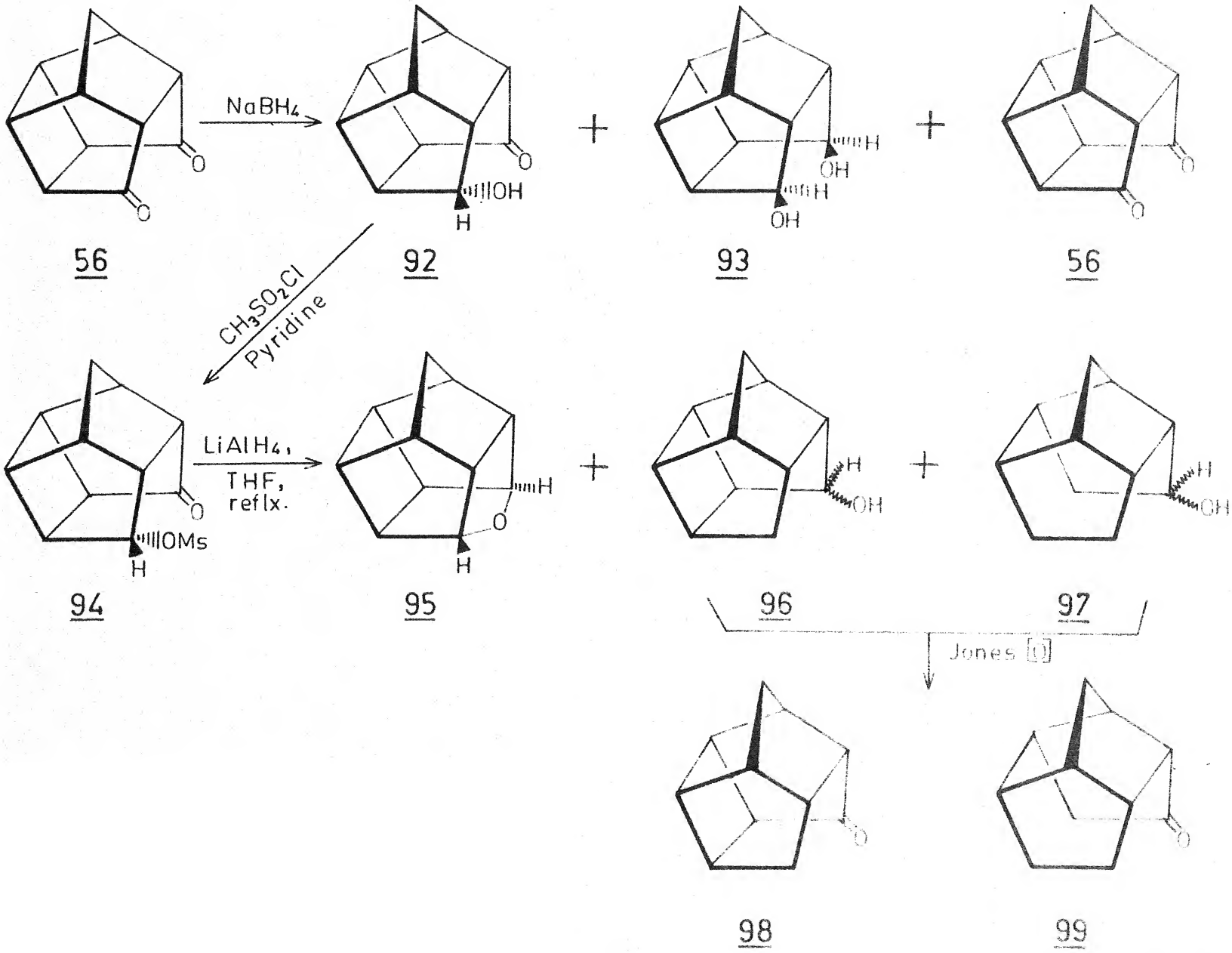
Scheme I . 13



Reaction with methanesulphonyl chloride in pyridine gave keto-mesylate (94), m.p. 105-107°. (IR , ν_{max}: 1750 carbonyl, 1345 and 1175 cm^{-1} mesyloxy). Acetolysis of the keto-mesylate (94) under forcing conditions led to a complex and intractable mixture of products. Also, reductive elimination of the mesyloxy group in 94 with the recently reported procedure[82] using sodium iodide, zinc dust in dimethoxy ethane (DME) or hexamethylphosphoric triamide (HMPA) gave a complex mixture of products from which no pure material could be isolated.

Finally, reaction of the keto-mesylate (94) with lithium aluminium hydride gave a mixture of three products, Scheme I.14. The major product, m.p. 228-230°C, was assigned the oxa-bird cage structure (95) on the basis of its ^{1}H NMR and ^{13}C NMR data. The ^{1}H NMR spectrum displayed a broad singlet at δ4.73 (2H) due to the protons attached to the carbon carrying the ether oxygen alongwith a complex multiplet between δ2.2 &3.0 (8H) and an AB-quartet at δ1.7 (2H, J = 11 Hz). Consistent with the formulation (95) is the ^{13}C NMR spectrum (Fig. I.1) showing six resonances at δ85.8(d), 54.5(d), 44.0(d), 43.9(t), 43.7(d), 41.6(d) with appropriate multiplicities.* The signal at δ85.8(d) is diagnostic of the H-C-O moiety. The two minor products turned out to be an intimate mixture, m.p. 207-208°C, IR , ν_{max}: 3460 cm^{-1}, hydroxyl, of alcohols 96 and 97 as indicated by the complex

*Off-resonance multiplicities in the ^{13}C NMR spectra of all the compounds reported here are indicated in parenthesis. The presence of (?) indicates that the multiplicity could not be figured out unambiguously.


NaBH4
OH
H
OH
H
OH
56
92
93
56
CH3SO2Cl
Pyridine
LiAlH4,
THF,
reflx.
OMs
H
H
H
OH
H
OH
94
95
96
97
Jones [O]
98
99

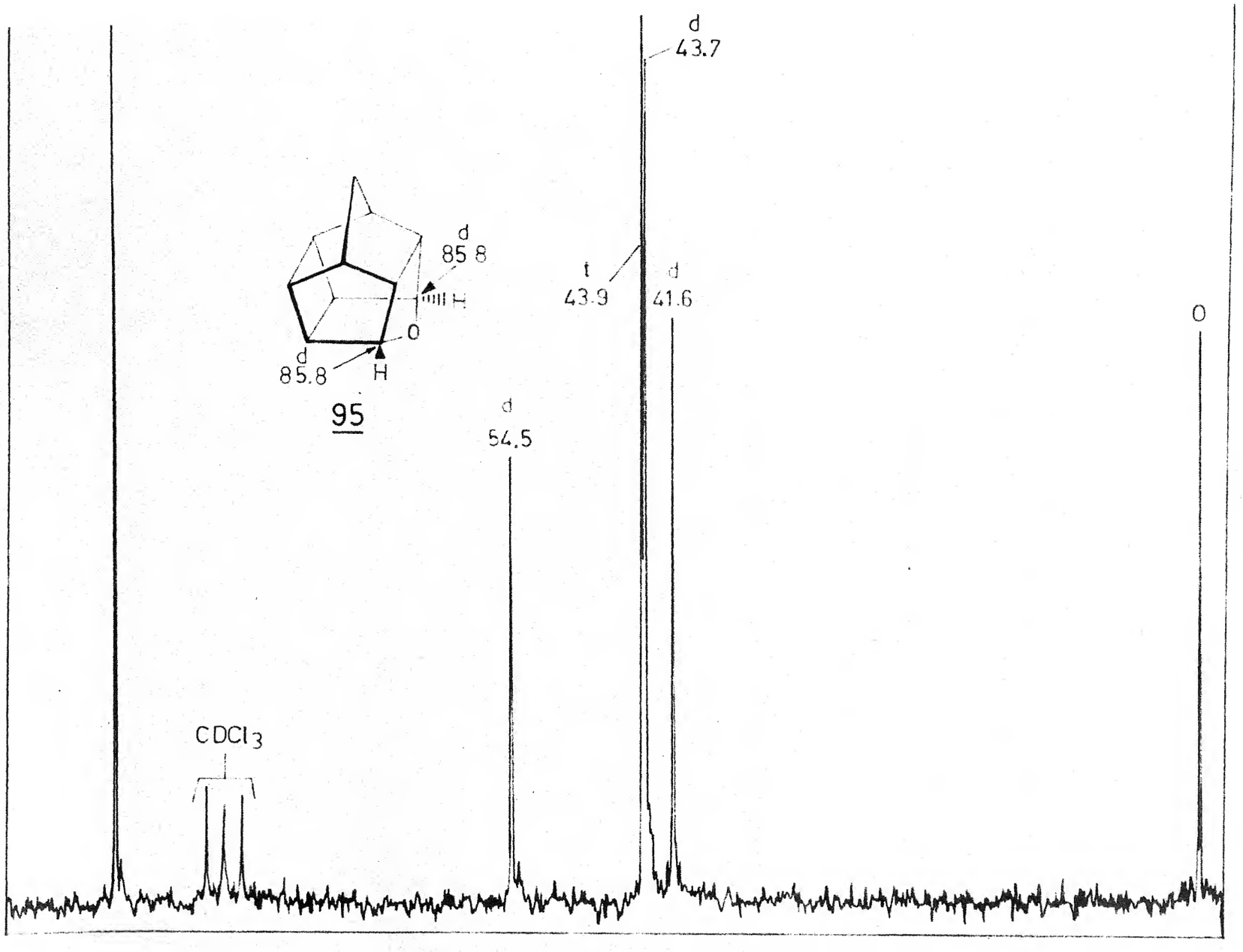


Fig. I.1 ^{13}CMR spectrum (22.64MHz) of 95

pattern of their ^{1}H NMR spectrum and the presence of twenty carbon signals in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum of the mixture of 96 and 97 exhibited two resonances at δ 74.3 and 73.9 due to two carbon atoms bearing hydroxyl groups. Jones oxidation[81] of the alcohol mixture furnished a solid ketone mixture (IR , ν_{max}: 1750 cm^{-1}, cyclopentanone), which could not be resolved by thin-layer chromatography. However, the ^{1}H NMR spectrum and ^{13}C NMR spectrum, in particular, of the mixture revealed their structures as 98 and 99. The ^{13}C NMR spectrum showed signals at δ 221.1(s), 220.4(s), 56.7(d), 53.1(?), 51.9(d), 50.3(?), 48.7(d), 48.5, 47.5(d), 47.4(d), 46.8(t), 44.6, 43.9(?), 43.4(?), 42.8(d), 41.7(d), 41.1(t), 39.6(d), 37.7(t), 36.9(d), 31.2(t). The presence of several CH_2's is consistent with the presence of 99 in the mixture. In particular, the signal at 37.7(t) reveals the presence of 98 and can be assigned to the carbon of CH_2 group at 4 position.* That the anticipated trishomocubanone (51) was not present in the mixture of ketones could be ruled out on the basis of ^{13}C NMR signals. The carbonyl carbon of 51 appears at δ 216.9 and shows only signals at δ 50.2, 41.1, 40.9, 35.5 due to its symmetrical structure.

With the availability of ether (95), it was decided to attempt its rearrangement to the trishomocubane framework.

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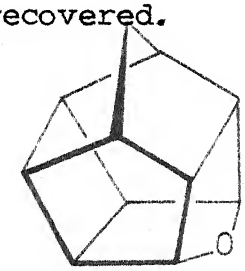
*^{13}C NMR parameters for various compounds belonging to the pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane skeleton are described in Chapter III.

Reaction of 95 with alane[83] (lithium aluminium hydride - aluminium chloride) in refluxing dry ether led to the formation of a crystalline mixture of alcohols, m.p. 207-208°C. Unfortunately, this mixture turned out to be identical to the mixture of alcohols obtained during the lithium aluminium hydride reduction of the keto-mesylate (94). This particular approach was therefore abandoned.

In another bid to rearrange the ether 95, it was refluxed with silver perchlorate in methanol. This was attempted in view of many examples in the literature[84,85] of the rearrangement of ethers undergoing reorganizations catalysed by transition metal ions. However, in the present case only the starting ether could be recovered.



95

$AgClO_4$, MeOH, reflux → No Reaction

Nevertheless, success was achieved by stirring the ether with methanesulphonic acid in methylene chloride for two hours at room temperature. A single, syrupy hydroxy-mesylate (101) was obtained in near quantitative yield. The IR spectrum of the hydroxy-mesylate (101) exhibited bands at 3400 cm^{-1}(hydroxyl), 1355 and 1190 cm^{-1} (methanesulphonoxy), and the ^1H NMR had diagnostic signals at δ4.15 (1H, s) and 4.85 (1H, s) ascribable

to the protons attached to the hydroxyl and mesyloxy groups, respectively. The methyl signal of the mesyloxy group appeared as a sharp 3H signal at δ3.05. These structural features were in reasonable agreement with the assigned structure (101), but could not rule out rigorously the unrearranged hydroxy-mesylate structure (102). The hydroxy-mesylate (101) on reduction with lithium aluminium hydride in dry tetrahydrofuran (THF) furnished the diol (103), m.p. 203-204°C, which was found identical with the diol, m.p. 203-204°C, reported recently by Barborak and Smith.[74] The ^{1}H NMR spectrum of the diol (103, Fig. I.2) was also distinctly different from the unrearranged endo, endo-diol (100, Fig. I.3) prepared from dione (56) according to literature procedure.[74]

Having discovered the right medium (methanesulphonic acid, methylene chloride) for effecting the smooth rearrangement of the pentacyclic system to the trishomocubane system, we decided to employ a more convenient precursor than the bird-cage ether (95). The compound of obvious choice was the symmetrical endo, endo-diol (100),[74,79] readily available via the lithium aluminium hydride reduction of the dione (56) (Scheme I.15). As anticipated, the diol (100) underwent a facile and quantitative rearrangement to the bifunctional trishomocubane-based hydroxy-mesylate (101). This hydroxy-mesylate proved to be a versatile material for elaboration into several trishomocubane derivatives. These transformations are summarized in Scheme I.16.

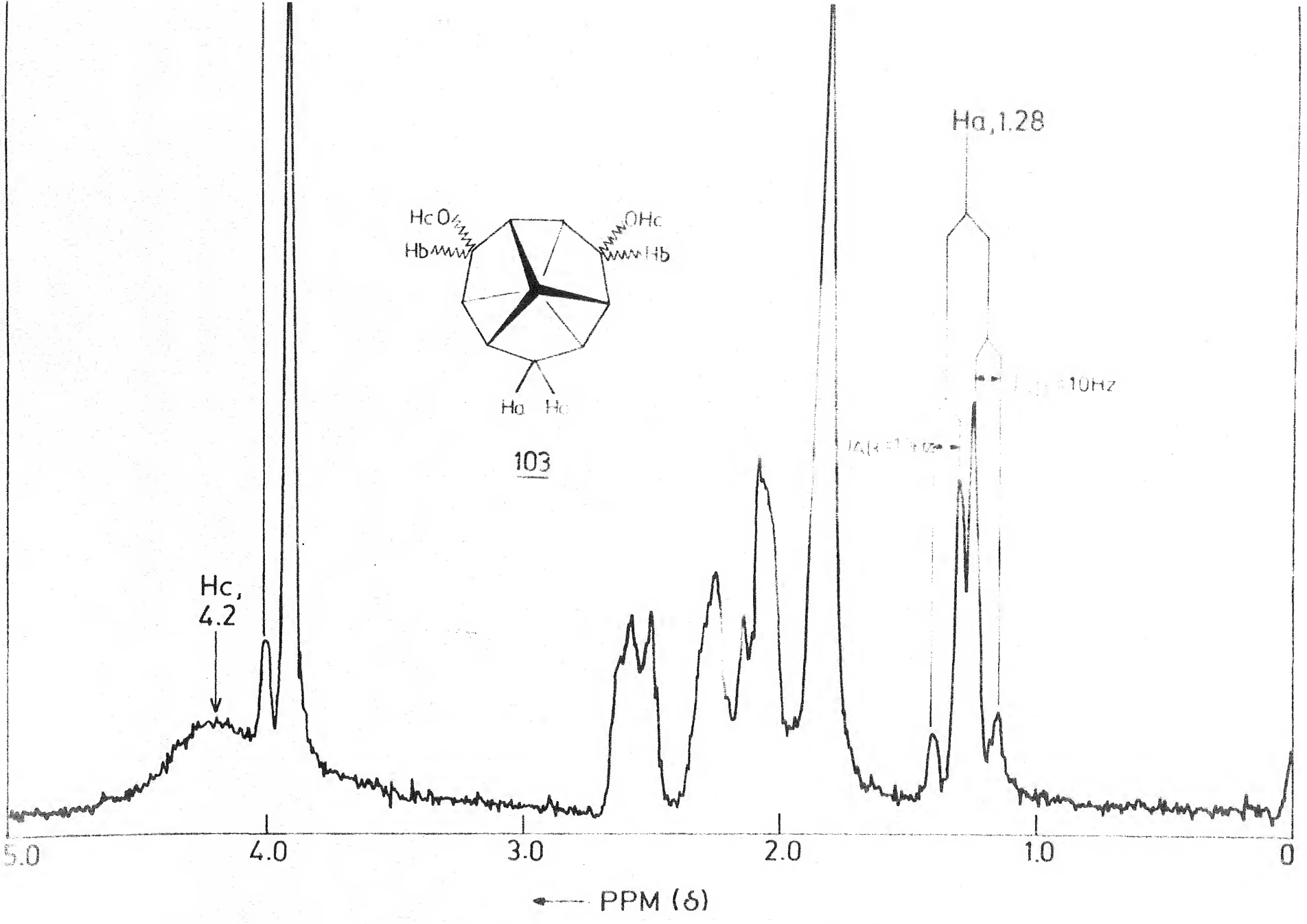
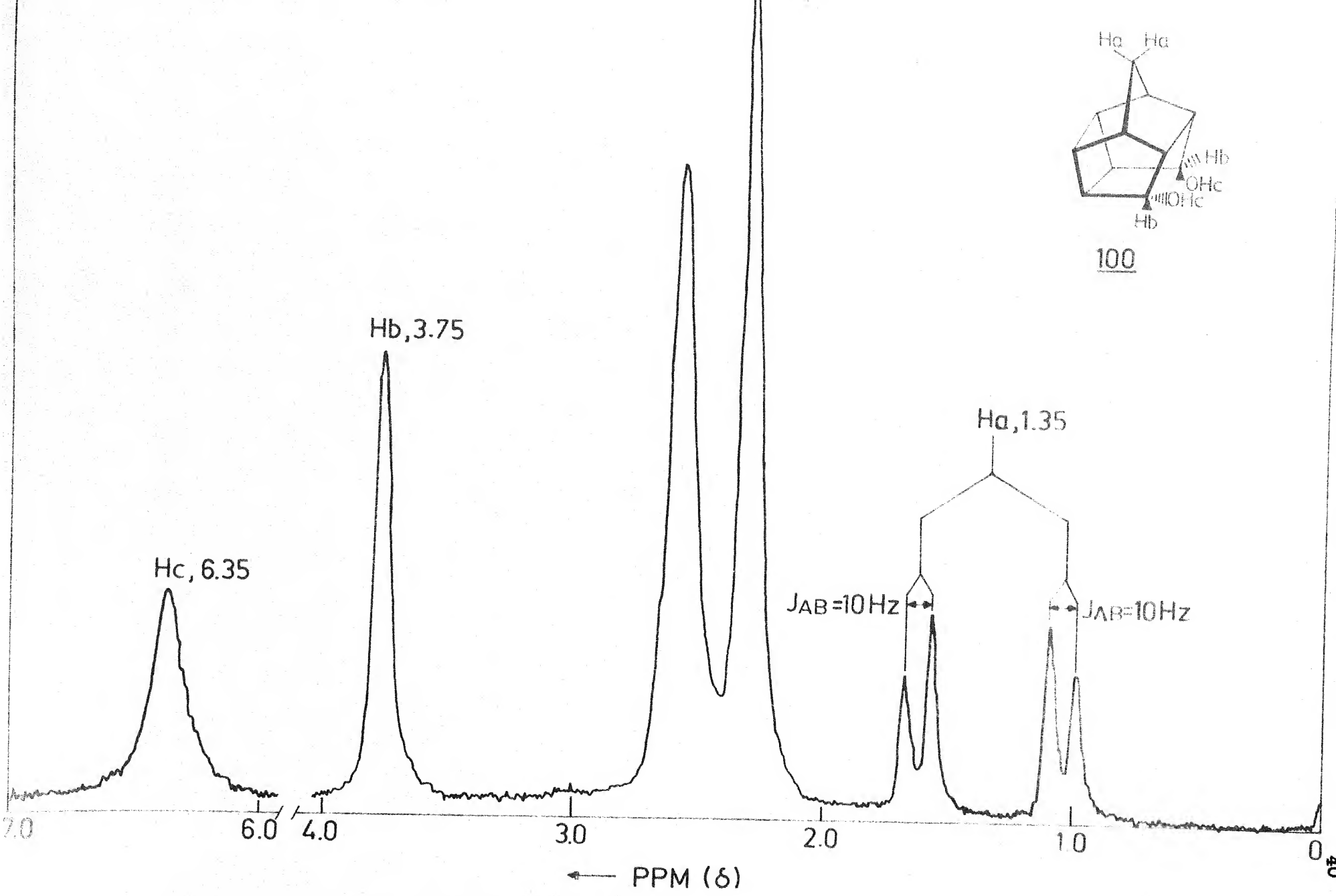


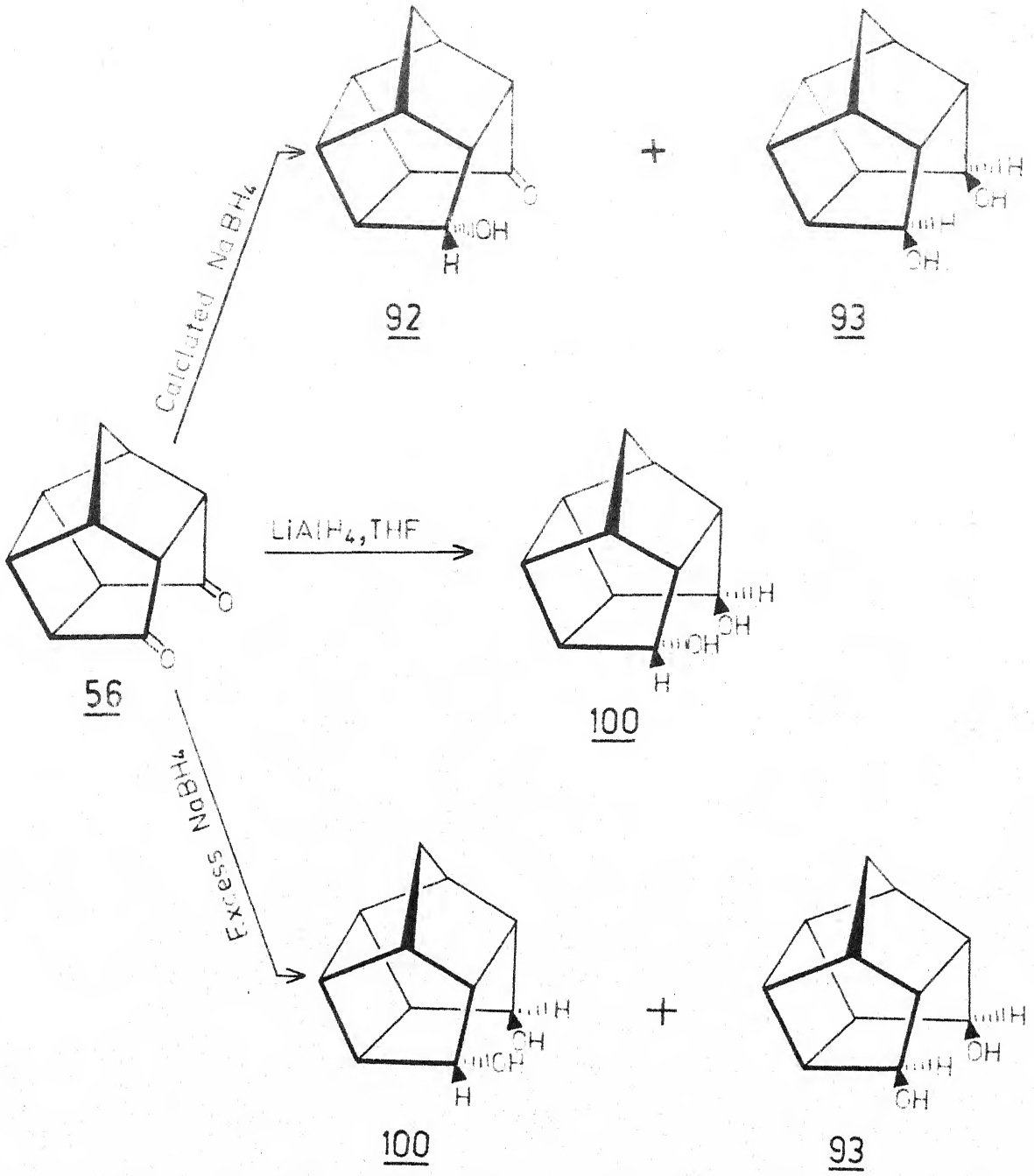
Fig. I.2 PMR spectrum (100.1MHz) of 103



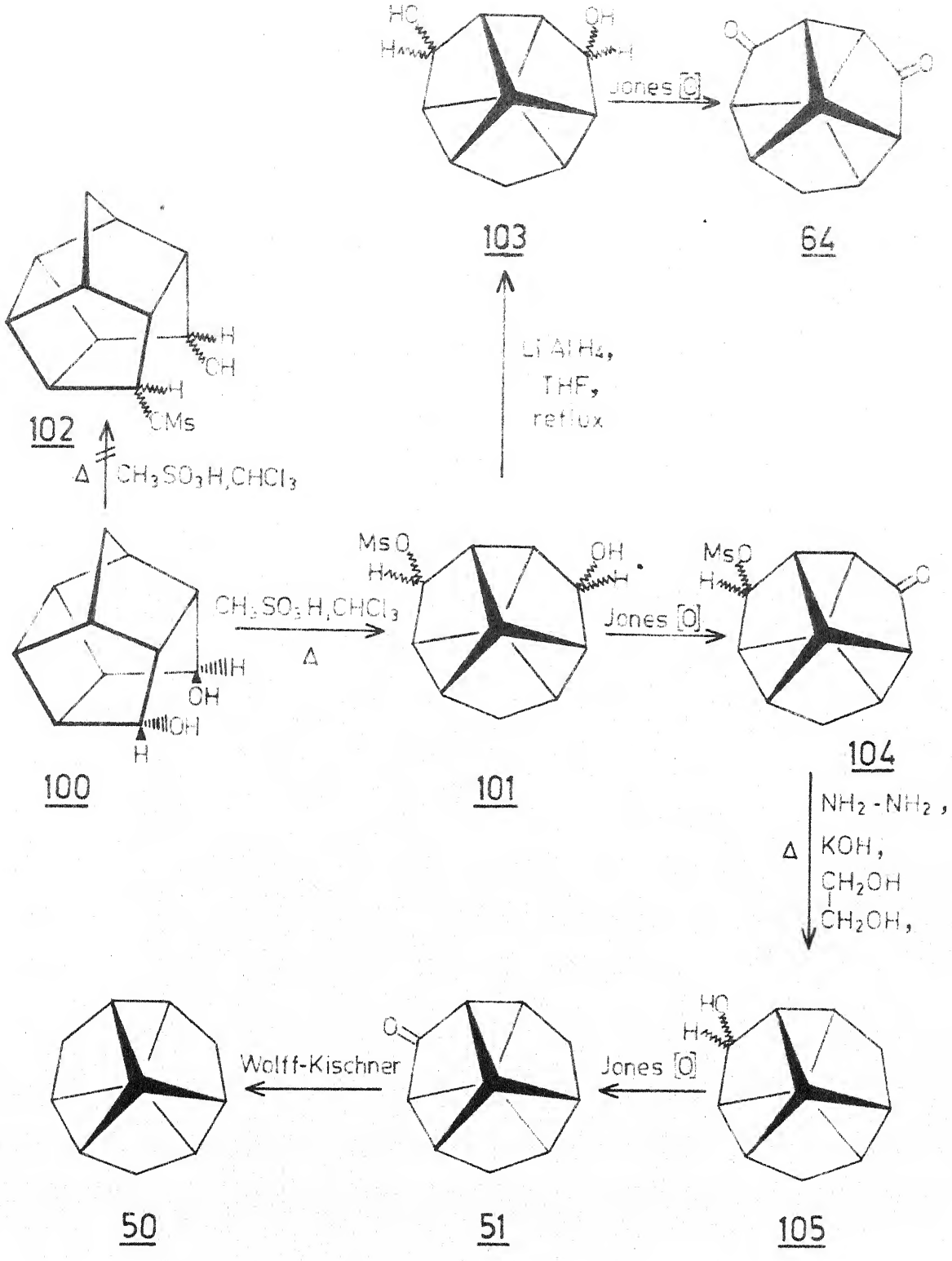
100

Fig. I.3 PMR spectrum (100.1 MHz) of 100

Scheme I.15



Scheme I.16


HO
H
OH
H
Jones [O]
O
O
103
64
Li Al H4,
THF,
reflux
H
OH
H
OMs
102
Δ
CH3SO3H,CHCl3
Ms O
H
OH
H
OH
H
100
CH3SO3H,CHCl3
Δ
Ms O
H
OH
H
101
Jones [O]
Ms O
H
O
104
NH2 - NH2 ,
Δ
KOH,
CH2OH
CH2OH,
HO
H
O
Wolff-Kischner
Jones [O]
50
51
105

Jones oxidation[81] of hydroxy-mesylate (101) furnished the keto-mesylate (104), m.p. 58-59°C in 98% yield. The IR spectrum (ν_{max}: 1760, carbonyl, 1355 and 1190 cm^{-1}, mesyloxy) and ^1H NMR spectrum (δ3.05, 3H, s and 4.85, 1H, s) were in agreement with its formulation. Wolff-Kischner reduction of the keto-mesylate (104), using Huang Minlon modification,[86] terminated the carbonyl group and simultaneously hydrolysed the mesyloxy group. This led to the direct isolation of (D_3)-trishomocubanol (105), m.p. 165-166°C. The IR and ^1H NMR spectra of 105 are as expected[66,67] and displayed in Figs. I.4 and I.5. Jones oxidation of 105 furnished (D_3)-trishomocubanone (51), m.p. 160-161°C. The IR spectrum (ν_{max}: 1770 and 1750 cm^{-1}, carbonyl), and ^1H NMR spectrum (δ1.50, 2H; 1.60 - 1.8, 4H, 2.40, 6H) of 51 are exhibited in Figs. I.6 and I.7. The sample of trishomocubanone was found identical to the various specimens of 51 reported by several other groups[66,76,77] during the course of the present study. Thus, 51 was prepared from 56 in five steps and in high yield without involving any chromatographic separation or purification step other than crystallization and sublimation. The parent (D_3)-trishomocubane (50) could be readily prepared from 51 *via* Wolff-Kischner reduction.

In another series of experiments, the hydroxy-mesylate (101) was reduced with lithium aluminium hydride to the diol (103), *vide supra*, and further oxidized with Jones reagent[81] to the crystalline dione (64), m.p. 213-214°C. The dione structure (64) follows

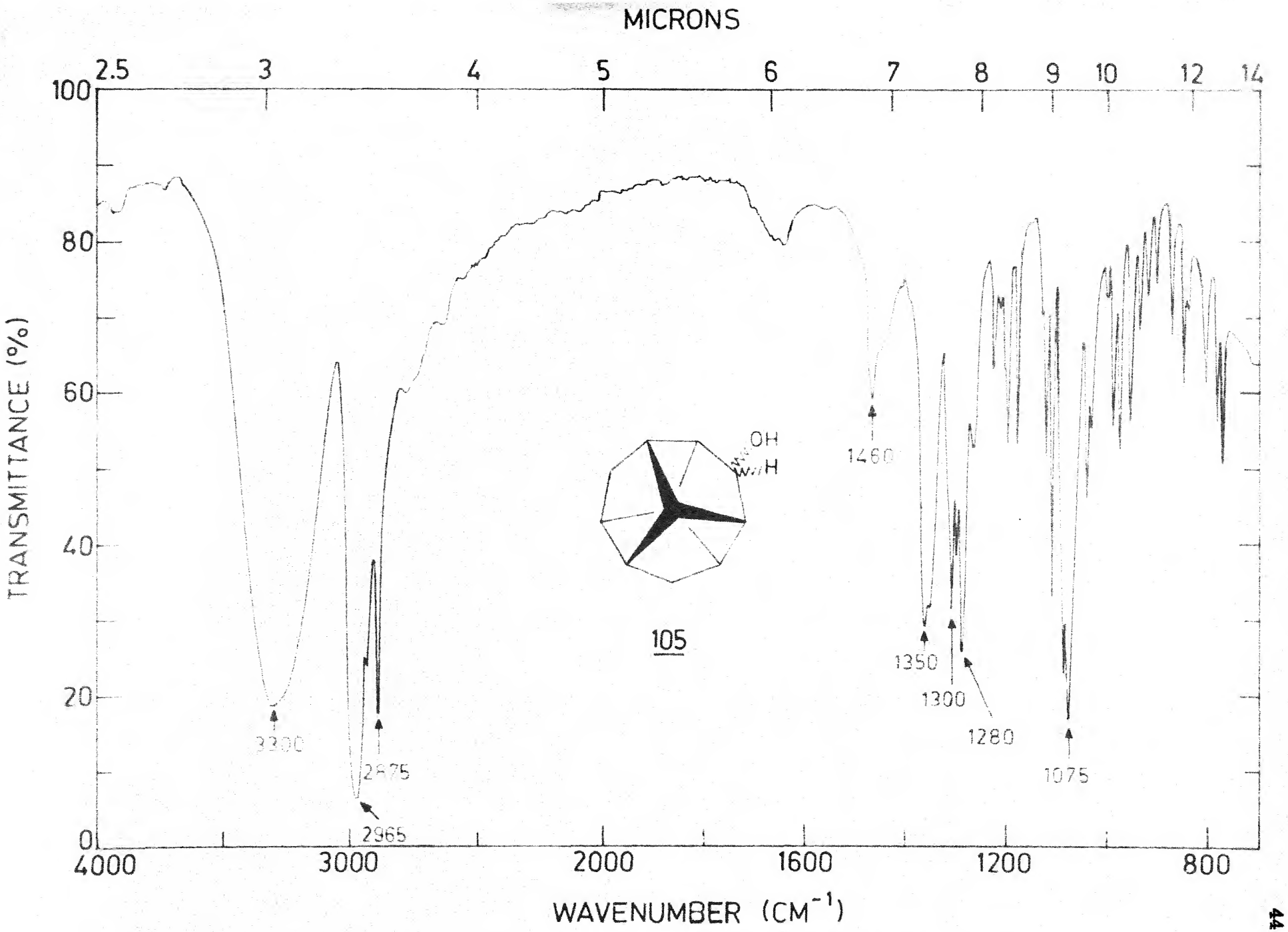


Fig. I.4 IR spectrum of TRISHOMOCUBANOL (105)

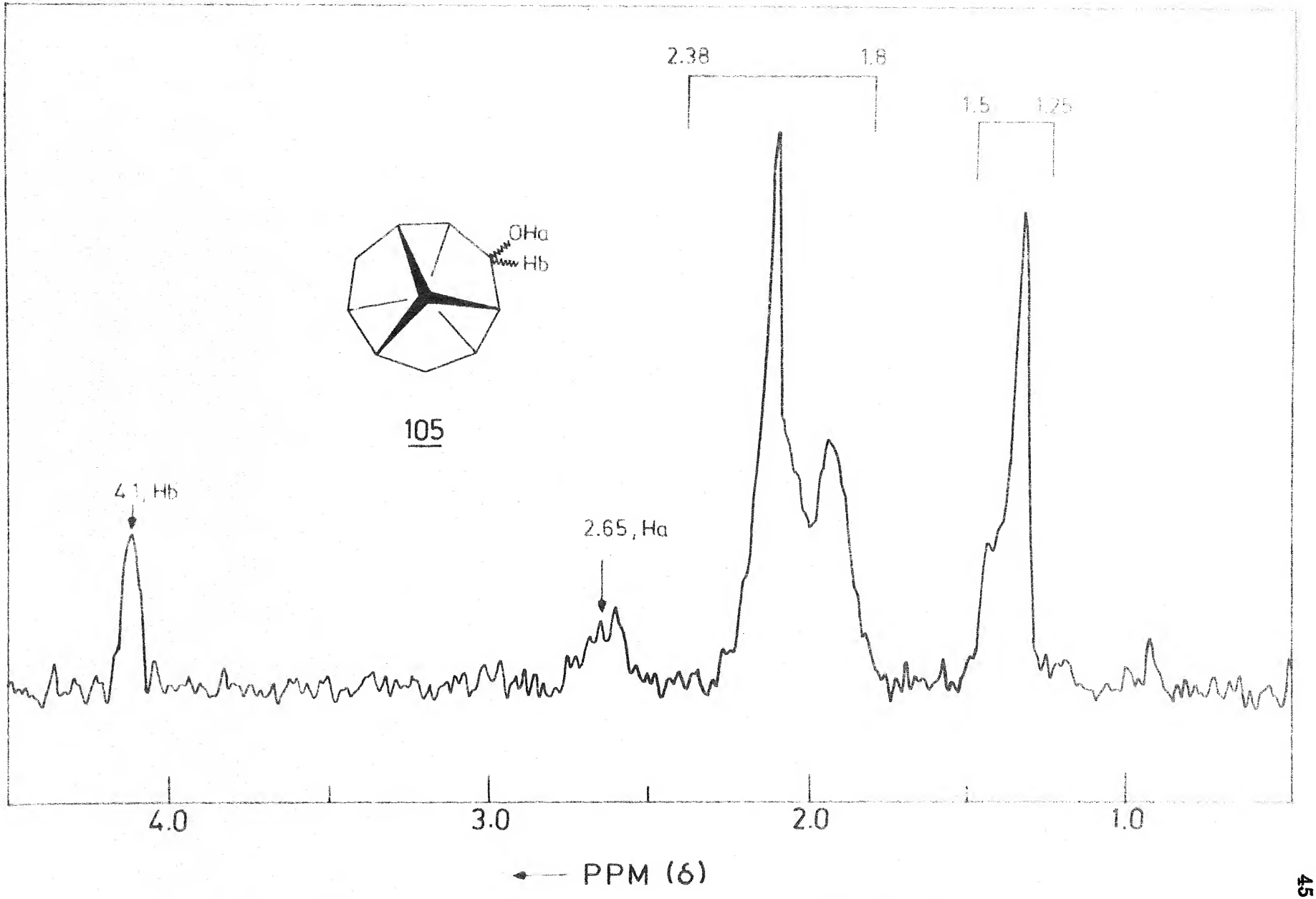


Fig. I.5 PMR spectrum (60MHz) of TRISHOMOCUBANOL 105

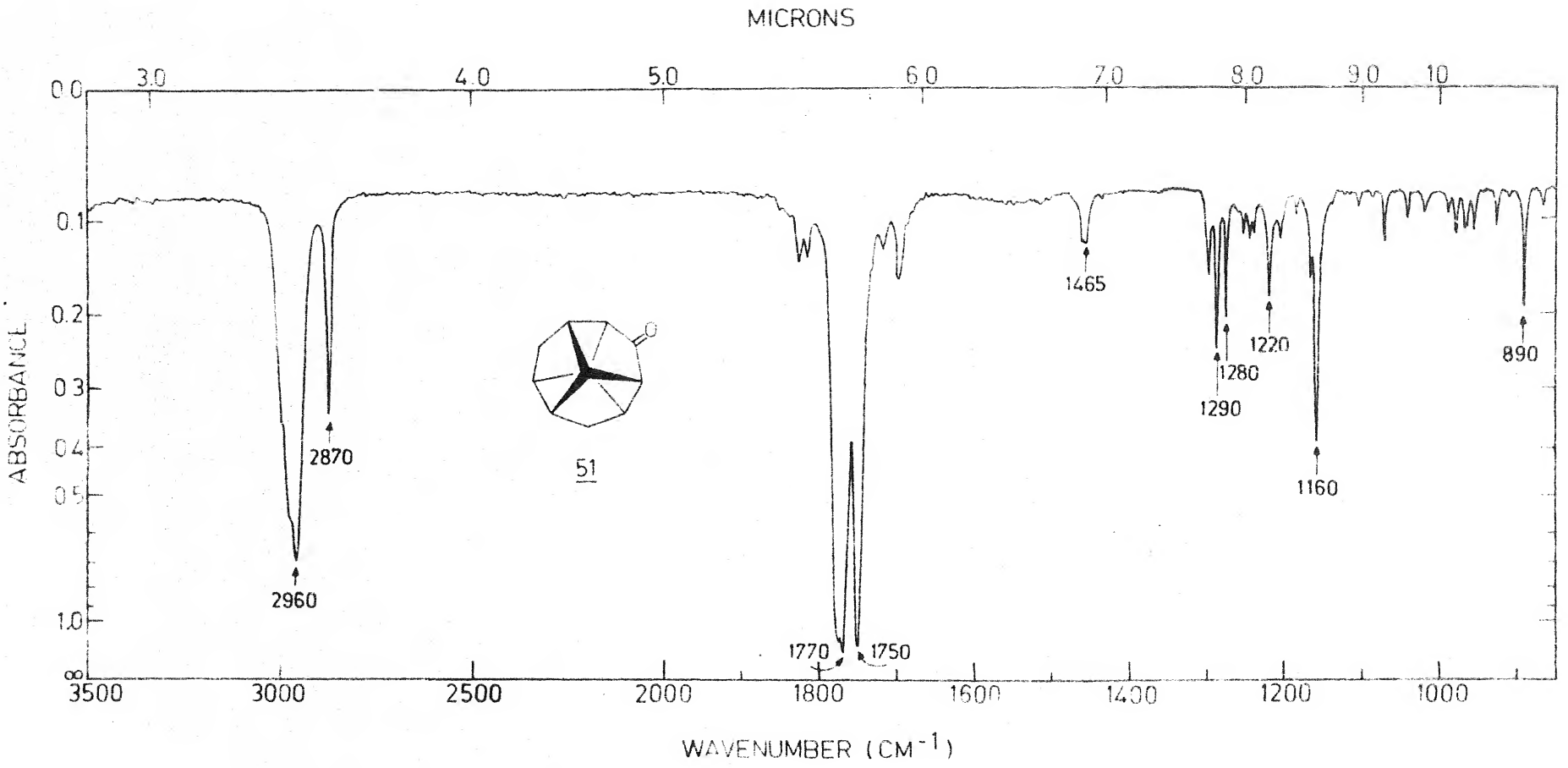


Fig. I.6 IR spectrum of TRISHOMOCUBANONE (51)

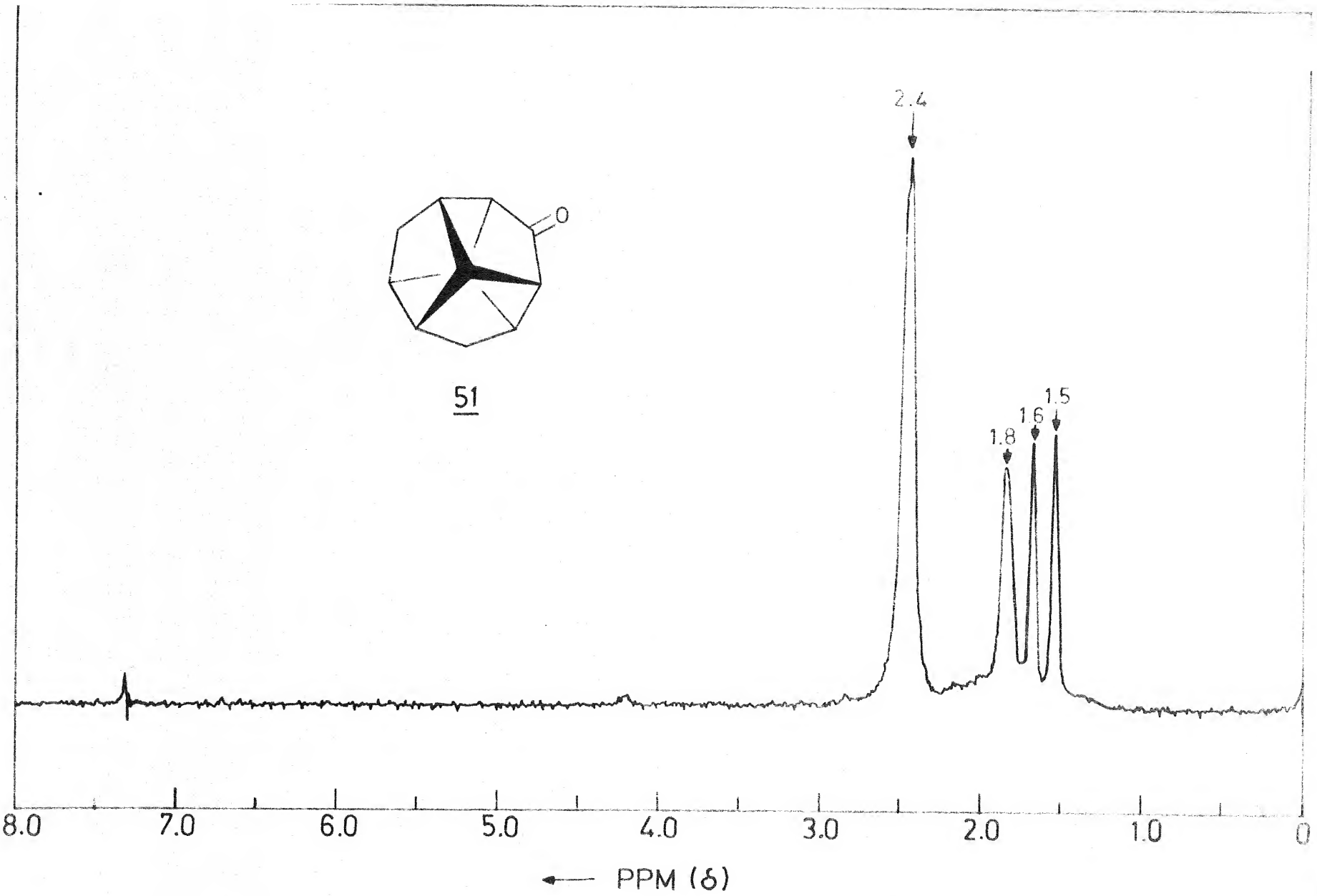


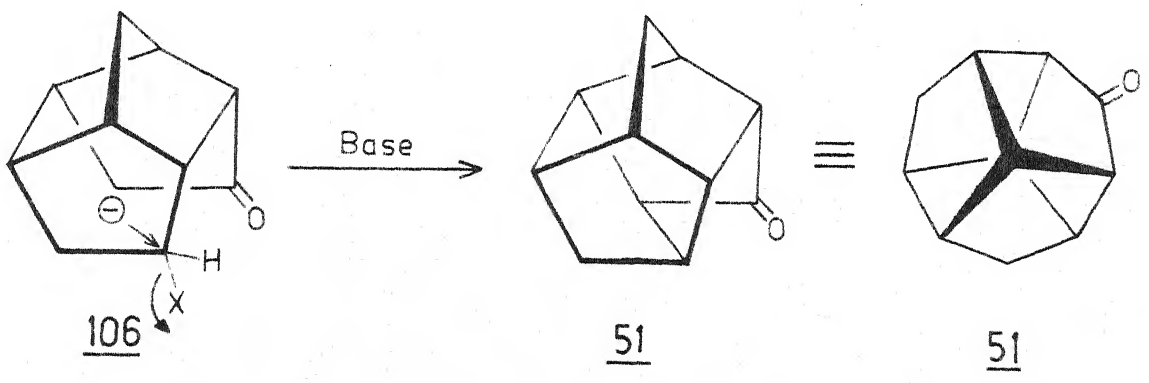
Fig. I.7 PMR spectrum (60MHz) of TRISHOMOCUBANONE (51)

from its IR spectrum (ν_{max}: 1785, 1765 cm^{-1}, carbonyl) and its relatively simple ^1H NMR spectrum (δ1.75, 2H, s; 2.19, 4H, br, s; 2.85, 4H, br, s)(Fig. I.8).

Thus, the procedure outlined here provides a rapid, simple and versatile entry to the trishomocubane derivatives in multigram quantities.

Earlier, we have considered the possibility of preparing the trishomocubane ring system through the intramolecular alkylation in a tetracyclic derivative of the type (106) (Scheme I.17) a sequence which eventually succeeded in the hands of Eaton's group.[33]

Scheme I.17



In order to prepare a suitable derivative of (106), we adopted the strategy indicated in Scheme I.18. The tetracyclic enone (79), indeed appeared to be a very versatile intermediate. Reaction of the dione (56) with zinc in hydrochloric acid, according to the procedure of Wenkert and Yoder,[87] resulted in the reduction of the strained cyclobutyl bond and formation of the tetracyclic dione (78), m.p. 255°C in high yield. Controlled, selective

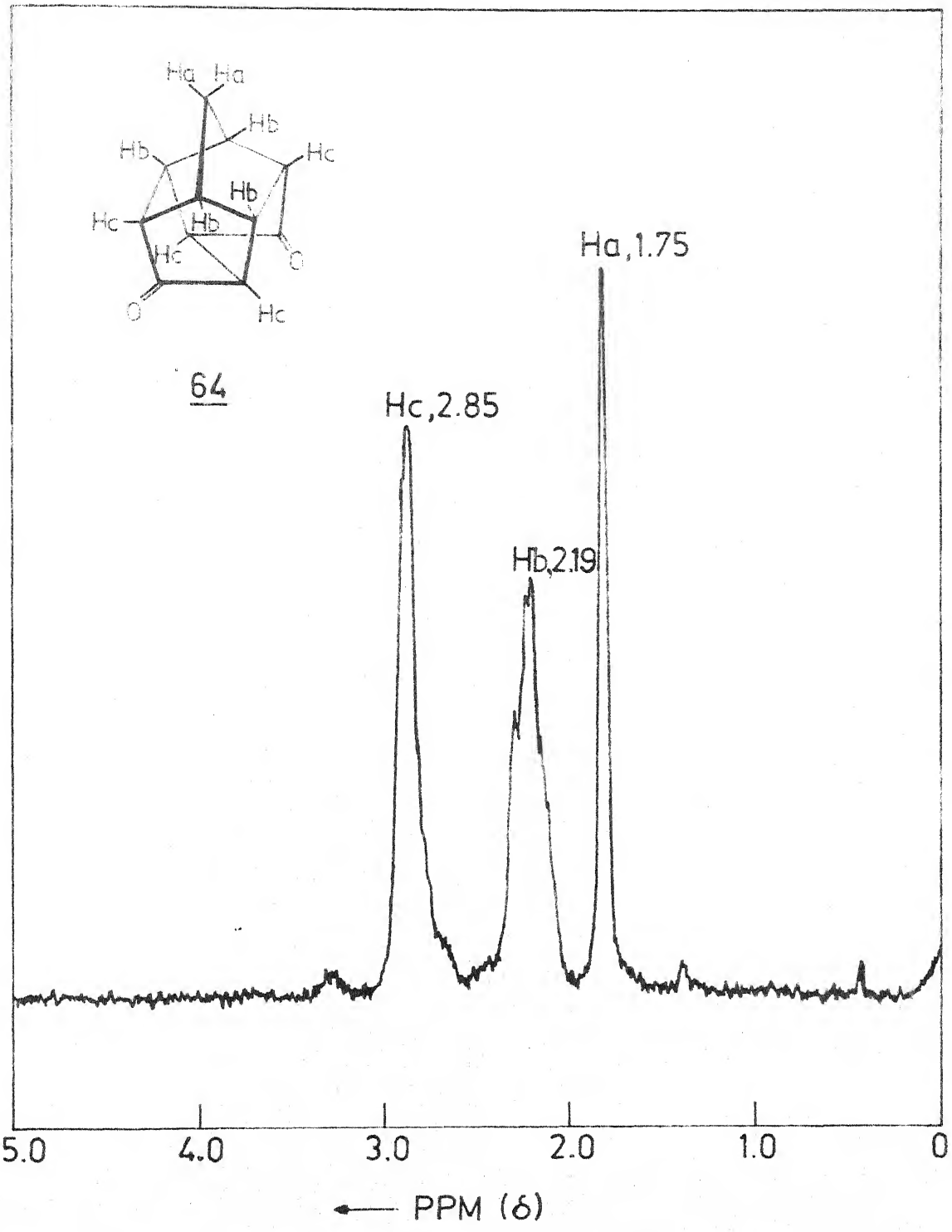
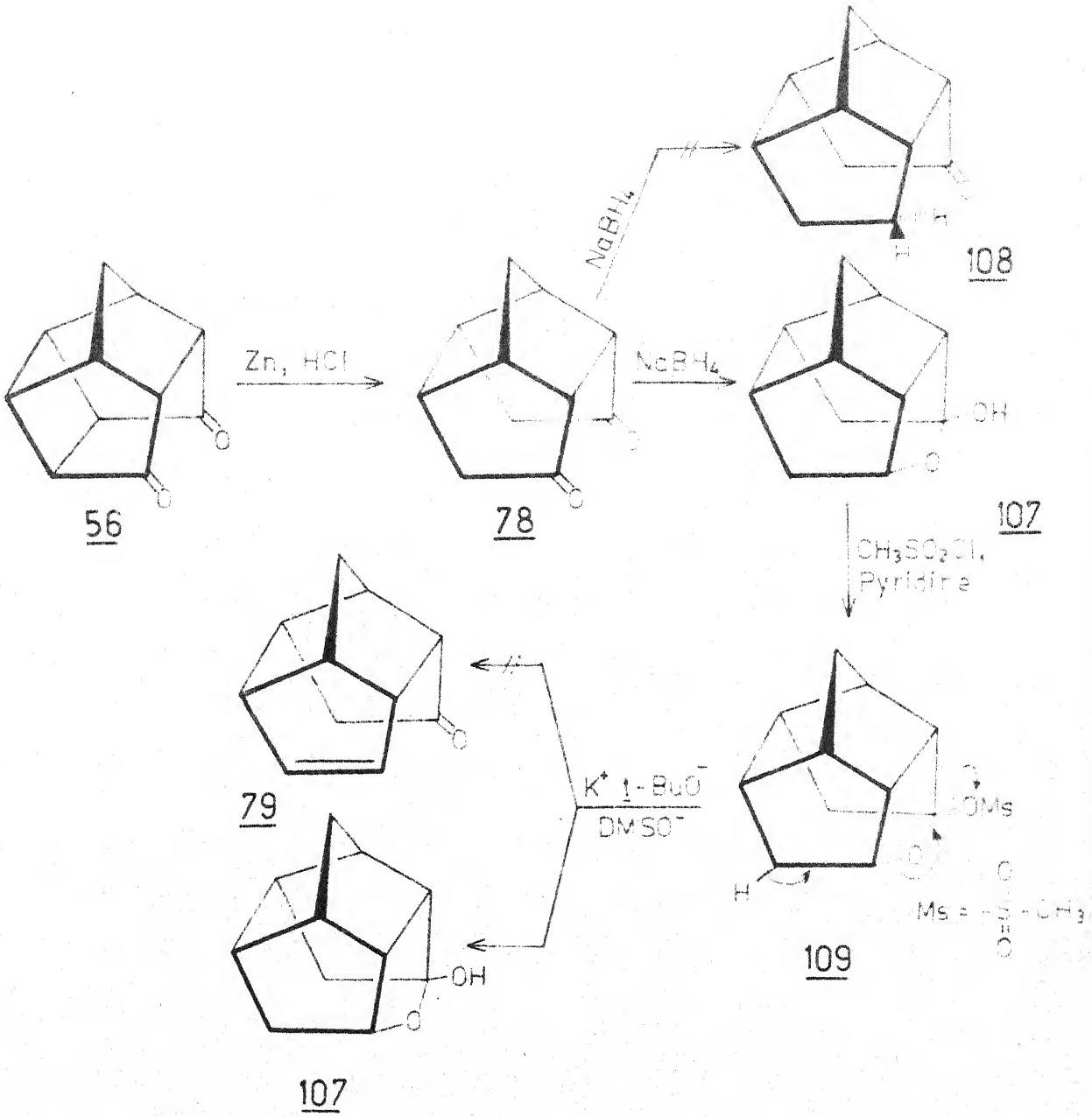


Fig. I.8 PMR spectrum (60MHz) of 64

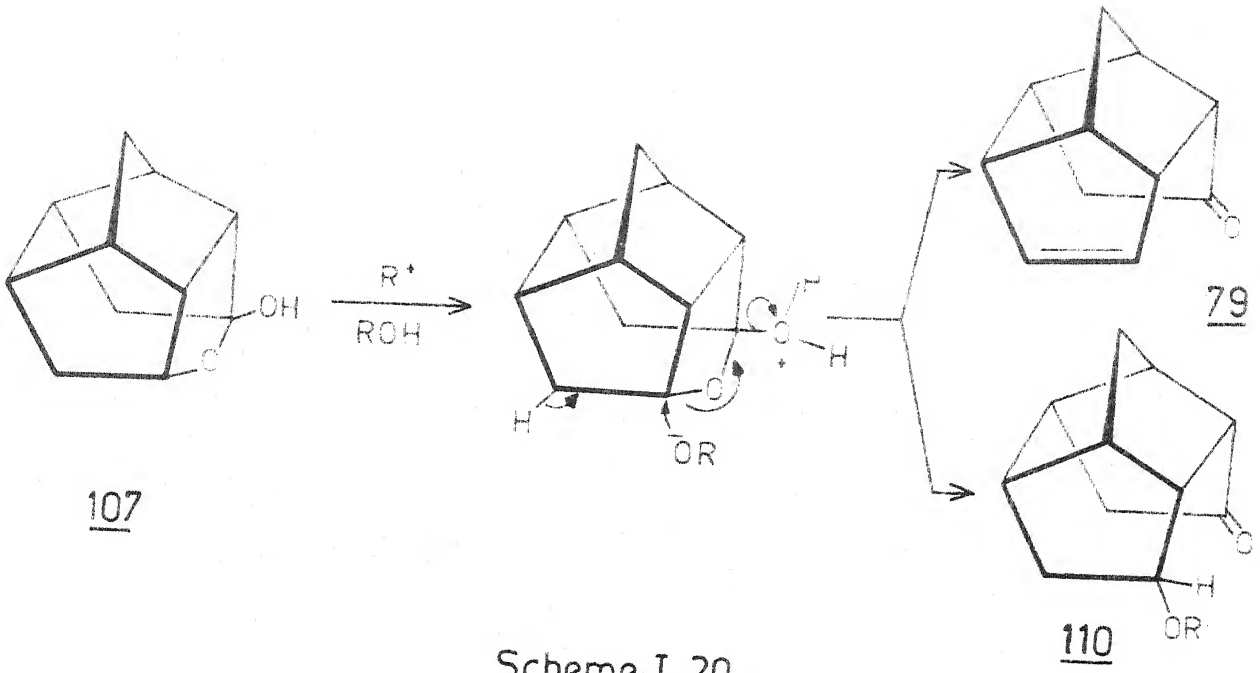
Scheme I.18


Zn, HCl
NaBH4
NaBH4
108
56
78
107
CH3SO2Cl,
Pyridine
K+ t-BuO−
DMSO
79
107
109
OMs
OH
H
Ms = CH3SO2

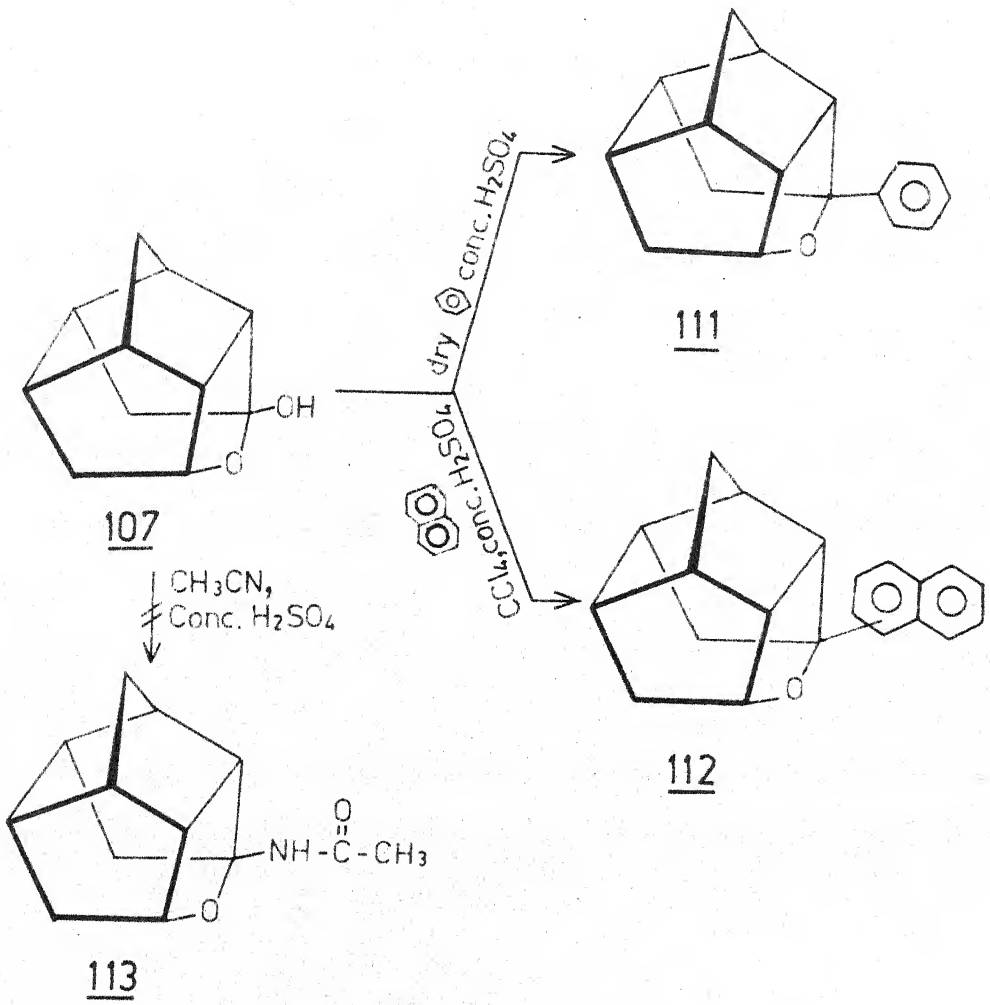
reduction of cleaved dione (78), with sodium borohydride in methanol furnished directly the lactol (107), m.p. 222°C, and the hydroxy-ketone (108) was not isolated. The structure of the lactol (107) follows from its IR spectrum which was devoid of any carbonyl absorption and in particular from the ^{13}C NMR resonances. The ^{13}C NMR spectrum revealed the presence of a quarternary carbon attached to oxygens at δ115.7(s) and another tertiary carbon attached to oxygen at δ81.1(d). The other carbon signals at δ58.7(d), 53.9(d), 49.4(d), 47.6(d), 43.7(t), 42.3(d), 41.4(d), 38.1(t), 37.9(t) were in expected range. The lactol (107), with methanesulphonyl chloride in pyridine furnished the mesylate (109), m.p. 58-59°C. The mesylate structure was confirmed by the absence of carbonyl absorption and ^{13}C NMR signals at δ122.3 (s, O-C-OMs) and 83.1 (d, H-C-O). Reaction of mesylate (109) with freshly sublimed potassium tertiary-butoxide in dimethylsulphoxide (DMSO) led to the isolation of starting lactol (107), without giving any elimination product (79), Scheme I.18.

When the aimed elimination reaction of the mesylate (109) of the lactol (107) with potassium tertiary-butoxide failed to produce desired results, we tried for an acid-catalysed opening of the lactol (107) as shown in Scheme I.19. Reaction of the lactol (107) with p-toluenesulphonic acid or methanesulphonic acid in refluxing dry benzene was quite sluggish and only trace amounts of a product exhibiting aromatic protons in the ^{1}H NMR spectrum was obtained. However, when the reaction was repeated in the presence of catalytic amounts of concentrated sulphuric

Scheme I.19



Scheme I.20



acid (Scheme I.20), a near quantitative yield of a crystalline product, m.p. 108-109°C, was obtained. The elemental analysis (M^+ 238, $C_{17}H_{18}O$) and ^1H NMR spectrum (Fig. I.9, δ7 - 7.5, 5H, m) of the product clearly established the incorporation of a mole-molecule of solvent during the reaction. The structure 111 for this product was deduced on the basis of ^1H NMR signal at δ4.75 (1H, t, J = 5 Hz) due to a proton attached to the ether oxygen, and the signals at δ83.4(d) and 93.9(s) in the ^{13}C NMR spectrum (Fig. I.10) due to carbon attached to oxygen and the carbon attached to both oxygen and an aromatic ring, respectively. The presence of the latter signal and its singlet multiplicity in off-resonance spectrum clearly revealed the substitution of the phenyl group at the bridgehead position. The other characteristic ^{13}C NMR signals consisted of aromatic carbon atoms at δ146.8(s), 128.0(d, 2C), 126.2(d, 2C) and 124.7(d). The mass spectrum, in conformity with the assigned structure 111, showed prominent fragments at m/e 77 and m/e 105 due to loss of C_6H_5 and C_6H_5CO, respectively.

To further probe the generality of the bridgehead substitution reaction, lactol (107) was reacted with naphthalene in the presence of concentrated sulphuric acid in refluxing carbon tetrachloride. This resulted in the isolation of a naphthalene substituted product (112), m.p. 102°C, in 50% yield, Scheme I.20. The structure 112 follows from the ^1H NMR spectrum, which clearly showed the presence of the proton attached to the ether oxygen at δ4.78 (1H, t, J = 7 Hz) besides aromatic proton multiplet

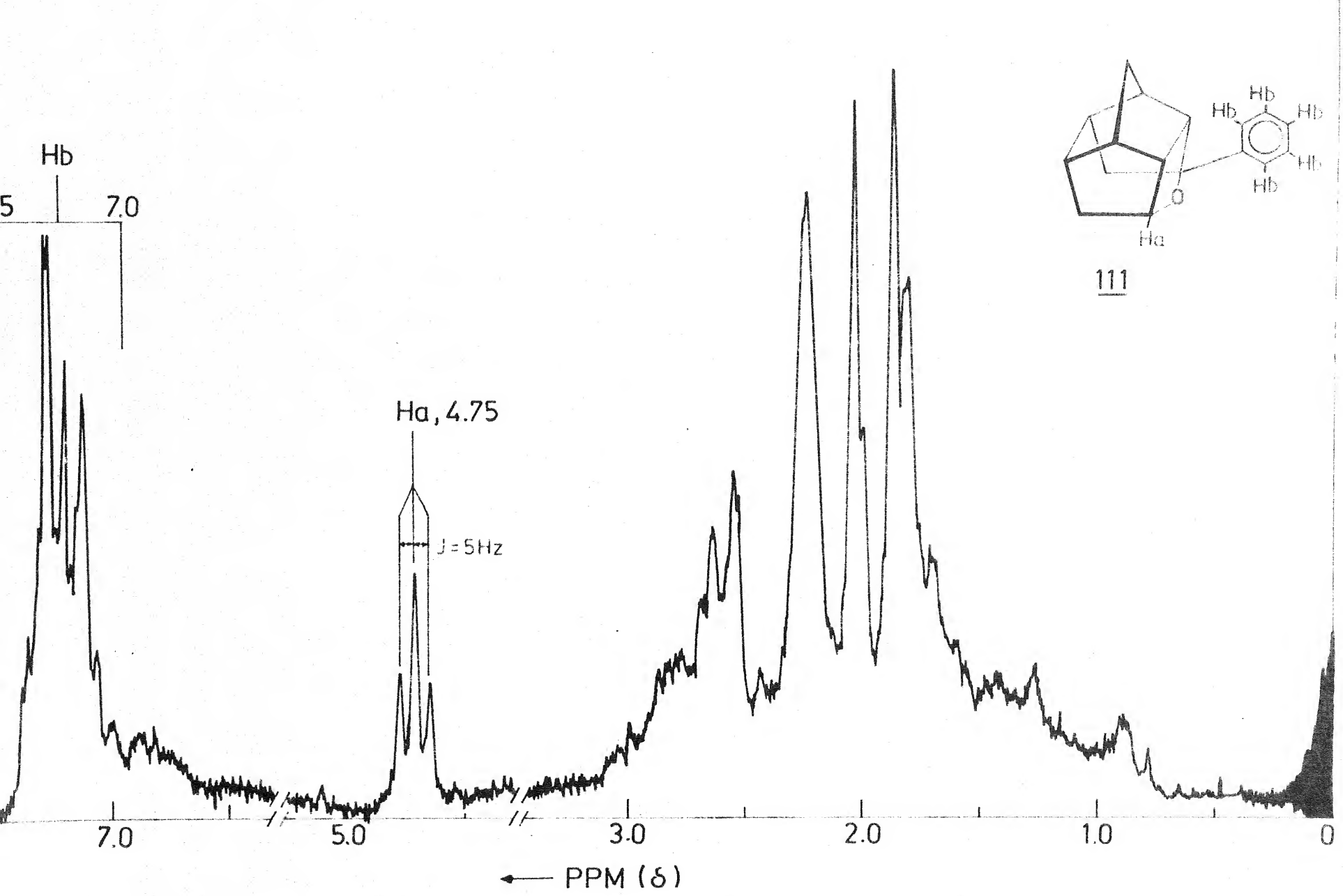


Fig. I.9 PMR spectrum (90MHz) of 111

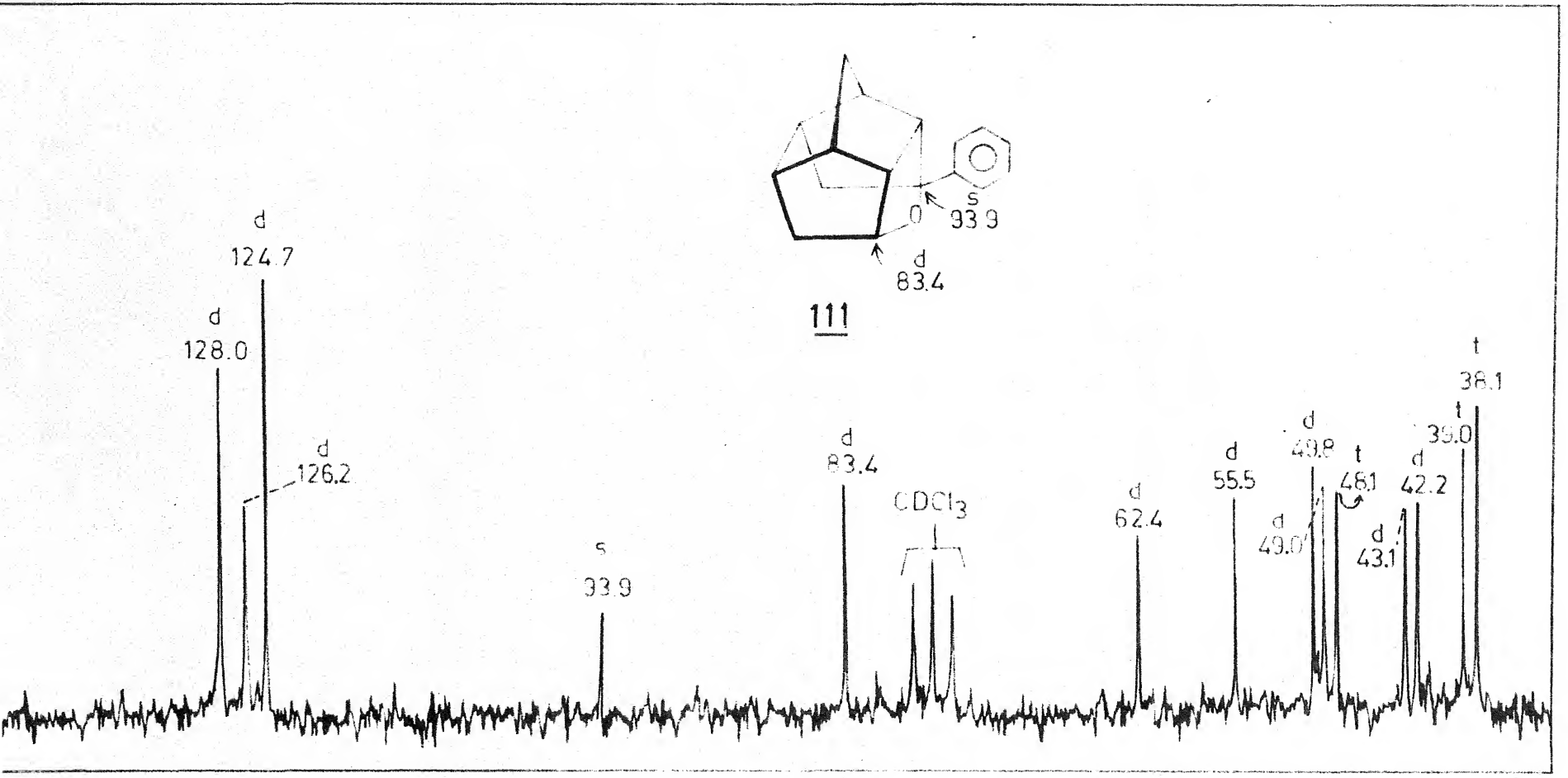


Fig. I.10 ^{13}CMR spectrum (22.64MHz) of 111

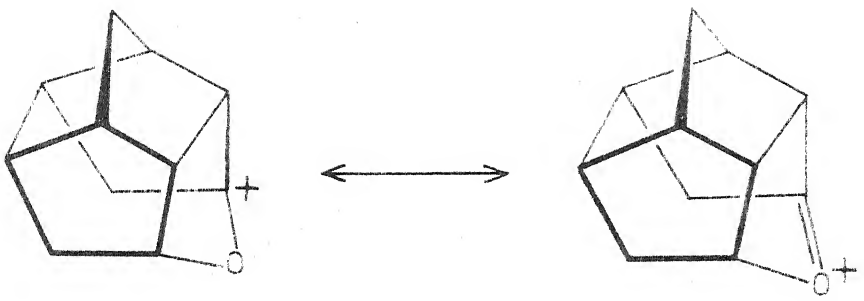
between δ7.15 and 8.7. When the reaction was carried out in acetonitrile and concentrated sulphuric acid extensive polymerization occurred and the corresponding amide (113) could not be isolated.

The formation of 111 and 112 from lactol (107) could be considered as arising through the intermediacy of bridgehead carbonium ion (114), Scheme I.21. However, this ion is unlikely to have much stabilization due to 115 because of unfavourable strain factors. Alternately, formation of 111 and 112 could be considered as proceeding via the electrophilic attack of a ring opened hydroxy carbonium ion (116) on the aromatic ring followed by recyclization, Scheme I.22.

To explore the validity of Scheme I.22, we studied the acid catalysed rearrangement of dione (56) and the pentacyclic ketol (92) under the conditions analogous to those of 107 to 111 conversion, to see if phenyl substituted products are formed. While the dione (56) remained unchanged during the reaction conditions, the reaction of 92 adopted a different course.

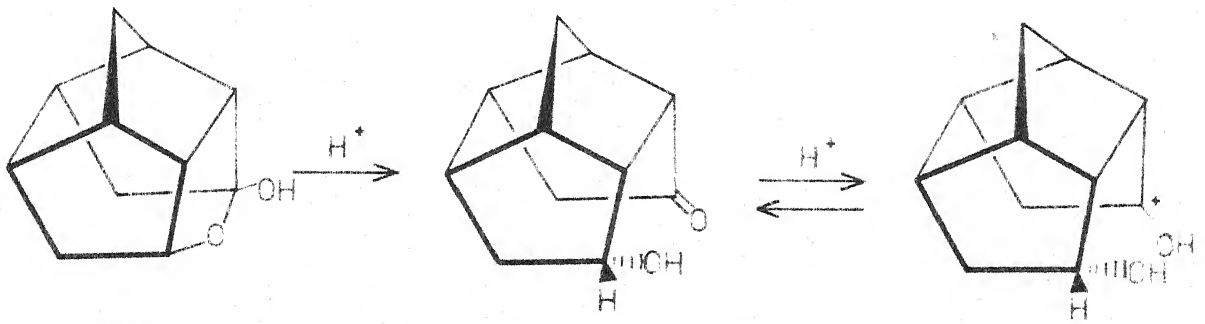
Reaction of the ketol (92) with catalytic amount of concentrated sulphuric acid in refluxing benzene led to the isolation of a white crystalline compound (118), m.p. 202-203°, in high yield, bearing an oxa-bird cage structure. The compound was found to be homogeneous by High Pressure Liquid Chromatography (HPLC) analysis. The dimeric nature of the product was evident from its mass spectrum (M^+ 334) and a doubled set of signals

Scheme I.21

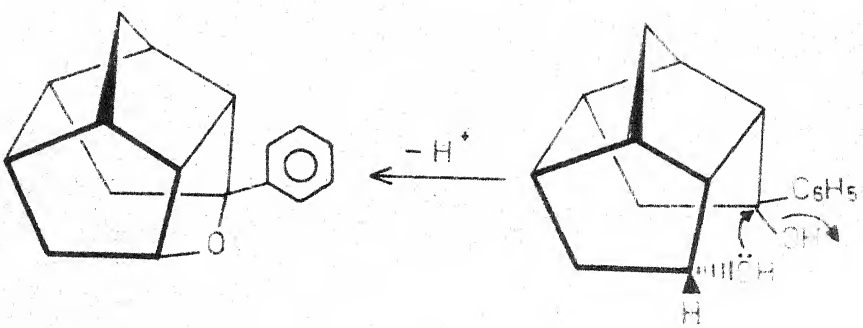


114 115

Scheme I.22



107 108 116



111 117

due to twenty-two carbons carbons in the ^{13}C NMR spectrum. The structure of 118 was deduced from its IR spectrum (ν_{max}: 1750 cm^{-1}, carbonyl) and ^{1}H NMR spectrum δ3.95 (1H, t, J = 4 Hz) and 4.52 (1H, t, J = 5.5 Hz) (Fig. I.11) due to two protons attached to ether oxygen in different environment. Further evidence for the structure 118 was forthcoming from the ^{13}C NMR spectrum (Fig. I.12). Besides the carbonyl carbon (δ215.8, s), the spectrum exhibited three deshielded carbons at δ122.1(s), 81.5(d) and 75.3(d). These could be assigned to the presence of O-C-O, H-C-O and H-C-OH type of functionalities, respectively. This data suggests 118 as the most likely structure for this unusual dimeric product. An alternate formulation (119) based on the trishomocubane skeleton could be ruled out on the basis of ^{13}C NMR chemical shifts of the methylene group. The chemical shift of the methylene group (triplet multiplicity in the off-resonance) for several pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane derivatives, resembling the structural features of the top half of the dimer, are given in Table I.2. The ^{13}C methylene carbon resonance for the trishomocubanes are also given in the table. It was evident that the ^{13}C signal at δ38.4(t) is diagnostic of the pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane system.

Finally, the mass spectra of 118 showed a strong m/e 159 peak which could account for the cleavage of the molecule into the two halves of similar mass, as shown in Scheme I.23.

The mechanism of formation of 118 from 92 could be visualized as depicted in Scheme I.24.

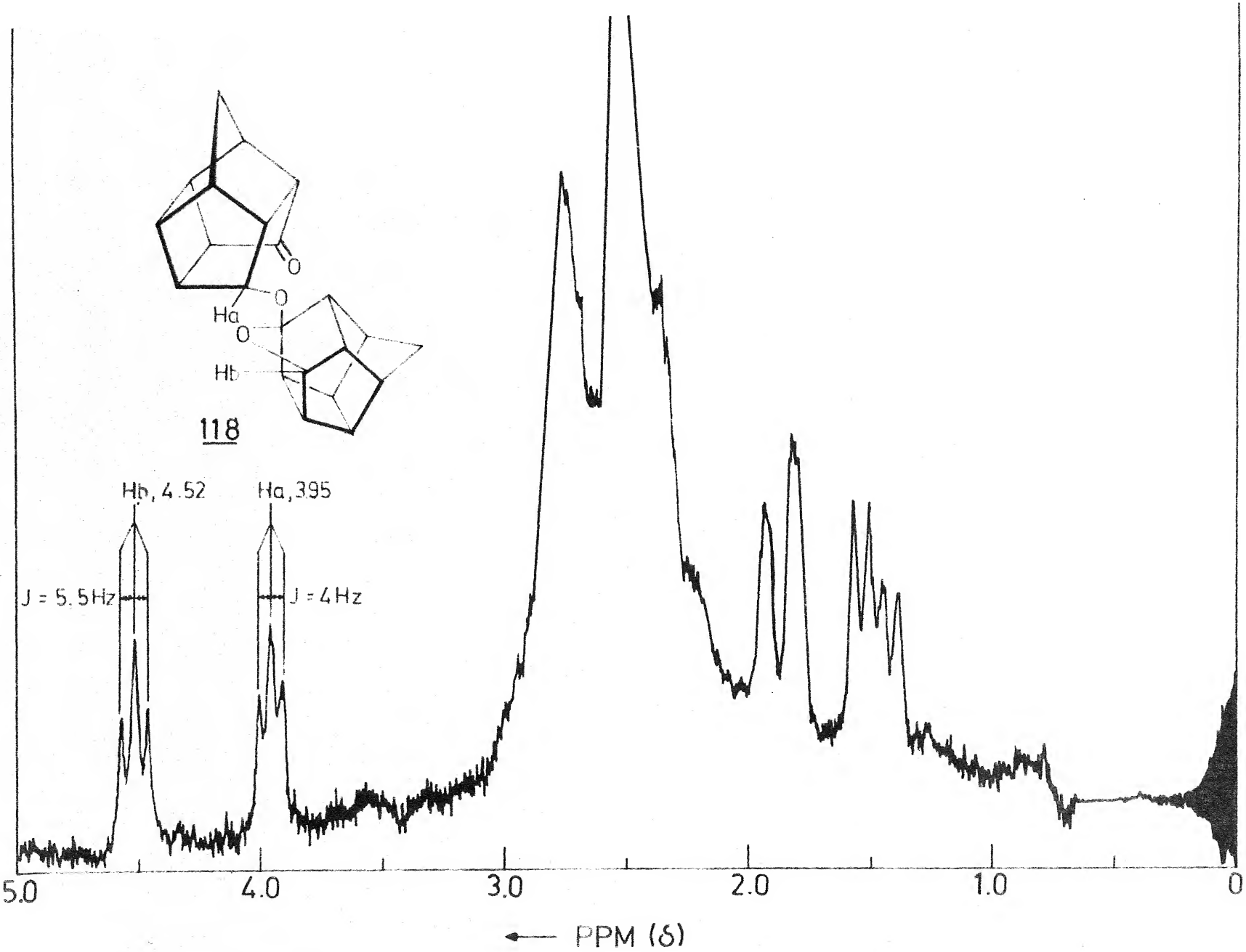
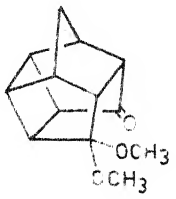
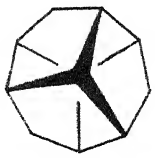
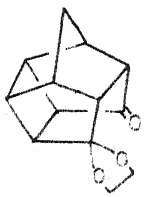
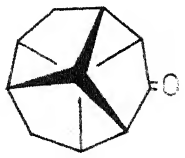
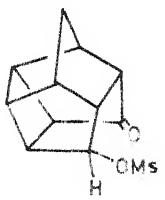
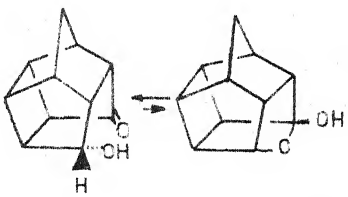
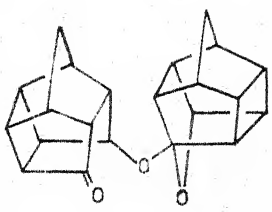
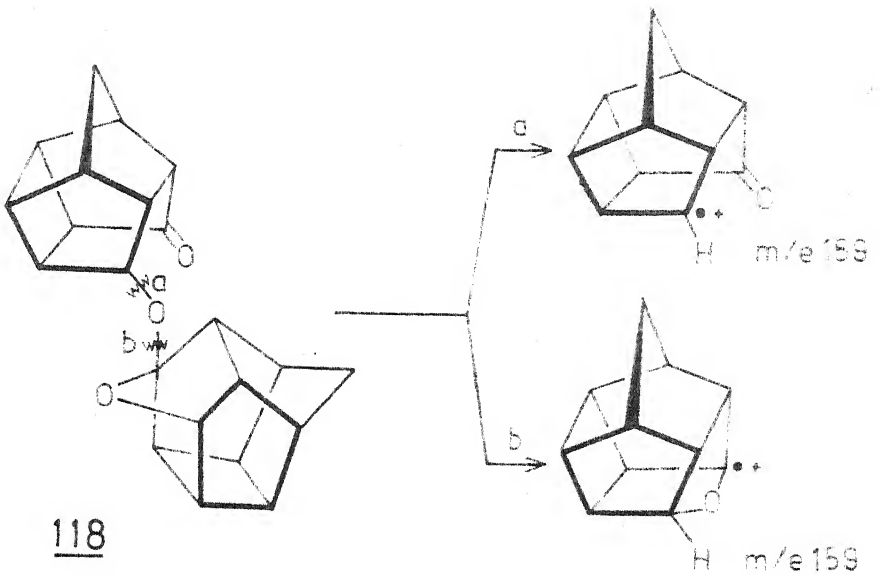


Fig. I.11 PMR spectrum (90MHz) of 118

BLE I.2 ^{13}CMR Chemical shifts of the Methylene carbons in Pentacycloundecane and Trishomocubane system.

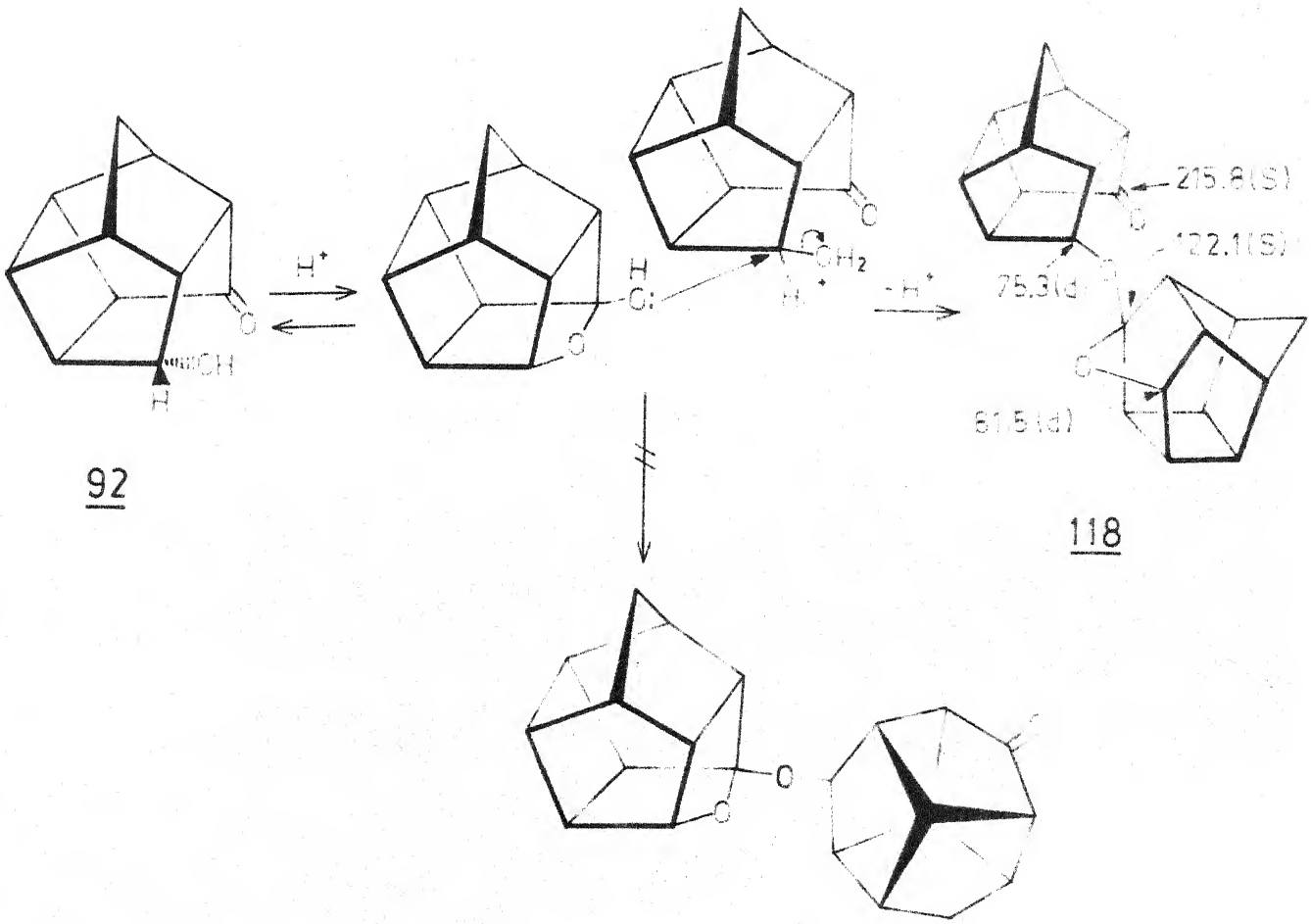
Structure	Chemical Shift(δ)	Structure	Chemical Shift(δ)
	38.4		33 3 ^{5E}
	38.8		35.5 ^{88}
	38.3		
	38.5		
	38.4		

Scheme I.23



118

Scheme I.24



92

118

I.4 EXPERIMENTAL SECTION

Melting points and boiling points are uncorrected. Melting points were taken in capillaries on a Thomas-Hoover melting point apparatus. Boiling point refers to oil-bath temperature in the case where short path bulb to bulb distillation was carried out. The petroleum ether corresponds to the fraction whose boiling point lies between 60-80°C. All solvent extracts were dried over anhydrous sodium sulphate. Infrared spectra were recorded on a Perkin-Elmer Model-137B and Perkin-Elmer Model-247B spectrophotometer as neat liquids or solids as KBr discs. PMR spectra were obtained on approximately 10-15% solutions in CCl_4, $CDCl_3$, or DMSO-d_6 on Varian A-60D or Varian XL-100 spectrometer. The chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ0.00) as an internal standard. The ^{13}CMR spectra were recorded in $CDCl_3$ using Bruker WH-90 spectrometer operating at 22.64 MHz. Chemical shifts are given with respect to internal tetramethylsilane. The abbreviations s, d, t, q, m and en in PMR and ^{13}CMR spectra refer to singlet, doublet, triplet, quartet, multiplet, and envelope respectively. Elemental analysis were carried out by Coleman Automatic, Carbon-Hydrogen Analyser. High Pressure Liquid Chromatography (HPLC) was performed in methanol solution on a μ-Porasil (P/N 27477) column using a Water-Associates' instrument.

Cyclopentadiene-p-benzoquinone adduct (73)

To an ice-cold solution of freshly sublimed p-benzoquinone (20 g, 0.18 mol) in dry benzene (50 ml) was added freshly distilled cyclopentadiene (12.3 g, 0.18 mol) with gentle swirling of the flask. After the addition was complete, the reaction flask was left aside at room temperature for 2 hr for crystallization. Filtration gave 28 g (88%) of the adduct (73) as pale yellow crystals, mp 76°C (lit.[80] 75-76°C).

IR spectrum (KBr), ν_{max}: 1670 (carbonyl), 835 and 750 cm^{-1}.

PMR spectrum ($CDCl_3$): δ1.4 ($-C\underline{H}_2$, 2H, s), 3.12 and 3.14 (C-H ring, 4H, pair of s), 5.94 (H-C=C-H, 2H, s), 6.4 (O=C-CH=CH-C=O, 2H, s).

Pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione (56)

A solution of the adduct (73, 15 g, 0.086 mol) in ethylacetate (200 ml) was purged with a slow stream of purified nitrogen for 25 min. The solution was then irradiated with a 450 W Hanovia medium pressure mercury arc lamp for 7 hr in a pyrex immersion well. Removal of solvent and direct crystallization from benzene-petroleum ether mixture furnished stout, white crystals of diketone (56). The yield was 13 g (87%), mp 243-244°C (lit.[79] 245°C).

IR spectrum (KBr), ν_{max}: 1750 cm^{-1} (carbonyl).

PMR spectrum ($CDCl_3$: δ1.7 ($-C\underline{H}_2$, 2H, q), 2.2-3.0 (C-H ring, 8H, en).

Pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione Monoethylene Ketal (84)

A mixture of diketone (56, 5 g, 28.8 mmol), ethylene glycol (1.8 g, 29.0 mmol), p-toluenesulphonic acid (0.07 g), and dry benzene (100 ml) was taken in a flask to which a Dean-Stark separator was attached. The solution was refluxed with good stirring for 5 hr. The reaction mixture was then cooled and poured slowly into ice-cold 10% aqueous sodium carbonate solution (50 ml). The solution was extracted with more of benzene (50 ml x 4) and washed with brine. After drying, solvent evaporation gave a colourless viscous liquid. Crystallization in solvent mixture of ether-hexane afforded 5.5 g (87%) of the monoketal (84), mp 73°C (lit.[33] 73.0 - 73.5°C).

IR spectrum (KBr), ν_{max}: 1750 (carbonyl), 1105 cm^{-1} (ketal).

PMR spectrum ($CDCl_3$): δ1.58 (1H, d, J = 10 Hz), 1.88 (1H, d, J = 10 Hz), 2.5 - 3.0 (8H, m), 3.91 (4H, m).

^{13}CMR spectrum ($CDCl_3$): δ214.7 (s), 114.0(s), 65.8(t), 64.6(t), 53.1(d), 50.8(d), 46.0(d), 42.9(d), 42.4(d), 41.6(d), 41.5(d), 38.8(t), 36.4(d).

11-Hydroxypentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one Ethylene Ketal (85)

The keto-ketal (84, 2.2 g, 10.1 mmol) was dissolved in distilled ethanol (25 ml). The solution was cooled in an ice-bath. A freshly prepared, cold solution of sodium borohydride

(0.76 g, 20.0 mmol) in water (17 ml) was added with stirring over 6 min. The reaction mixture was left for 2 hr in the ice-bath and then removed to room temperature and kept for 2 more hr. The mixture was put back into the ice-bath and 10 ml of 3% hydrochloric acid was added drop by drop. The solution was extracted with methylene chloride (25 ml x 3) and washed with brine. After drying, solvent evaporation gave a clear homogeneous oil (85, 2.2 g, 99%). It was distilled at 150°C, 1 mm Hg pressure.

IR spectrum (neat), ν_{max}: 3600 (hydroxyl), 1130 cm^{-1} (ketal).

Reaction of Trifluoroacetic acid with 11-Hydroxypentacyclo-[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one Ethylene Ketal (85)

To an anhydrous methylene chloride solution (10 ml) of the hydroxy-ketal (85, 0.25 g, 1.14 mmol), cooled in ice, was added trifluoro-acetic acid (1 ml) dropwise. After allowing it to stir for an hour and a half in an ice-bath, the reaction mixture was poured slowly into ice-cold sodium bicarbonate solution, and extracted with methylene chloride (15 ml x 3). The organic phase was washed once more with sodium bicarbonate solution, and then with brine. After drying, solvent evaporation gave 0.32 g (97%) of the trifluoroacetate (87), as a viscous oil.

IR spectrum (neat), ν_{max}: 1770, 1745 cm^{-1} (trifluoro-acetate).

Hydrolysis of the Trifluoroacetate (87)

To 0.30 g (1.04 mmol) of the trifluoroacetate (87) in methanol (10 ml) was added 20% aqueous sodium hydroxide solution. The solution was gently refluxed for 2 hr, cooled and poured into ice-cold 3% hydrochloric acid (10 ml). It was extracted with ether (15 ml x 3), and the organic layer was successively washed with dilute sodium bicarbonate solution and brine. After drying, evaporation of solvent yielded 0.2 g (87%) of a pale yellow oil (85).

IR spectrum (neat), ν_{max}: 3650 (hydroxyl), 1130 cm^{-1}(ketal).

Jones Oxidation of Hydroxy-Ketal (85)

To a solution of the hydroxy-ketal (85, 0.2 g, 0.91 mmol) in acetone (10 ml) was added dropwise Jones reagent, till the yellow colour persisted. After allowing the reaction mixture to stir for 2 hr at room temperature, it was poured into cold water. The aqueous solution was extracted with methylene chloride (10 ml x 3), washed with 10% sodium carbonate solution and brine. After drying, removal of solvent yielded 0.14 g (88%) of diketone (56), which was crystallized from benzene-petroleum ether mixture (60:40).

IR spectrum (KBr), ν_{max}: 1750 cm^{-1} (carbonyl).

The spectrum was superimposable to that of the diketone (56) obtained after photolysis.

Acetolysis of 11-Hydroxypentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]-undecan-8-one Ethylene Ketal (85)

To an acetic acid solution (7 ml) of the ketal (85, 0.25 g, 1.13 mmol) was added acetic anhydride (1 g, 9.8 mmol) and a few drops of boron trifluoride-etherate (0.05 ml) and the solution was gently refluxed for 2 hr. After cooling, the solution was poured carefully into saturated sodium carbonate solution, and extracted with ether (15 ml x 3). The ether extract was washed with dilute sodium bicarbonate solution, and then with brine. After drying, solvent was evaporated yielding 0.24 g (97%) of the keto-acetate (89) as a viscous oil.

IR spectrum (neat), ν_{max}: 1750, 1720 cm^{-1} (carbonyl and acetate).

Hydrolysis of the Keto-Acetate (89)

To 0.24 g (1.1 mmol) of the acetate (89) in methanol (10 ml) was added 20% aqueous sodium hydroxide solution. The solution was gently refluxed for 2 hr, cooled and poured into ice-cold 5% hydrochloric acid. The neutralized solution was extracted with ether (15 ml x 3), washed with dilute sodium bicarbonate solution, and brine. After drying, evaporation of solvent furnished a hydroxy-ketone (0.18 g, 92%).

IR spectrum (KBr), ν_{max}: 3350 (hydroxyl), 1740 cm^{-1} (carbonyl).

Jones Oxidation of the Hydroxy-Ketone: The hydroxy-ketone (0.18 g, 1.02 mmol) formed from the hydrolysis of keto-acetate (89)

was dissolved in acetone and Jones reagent was added dropwise, till in excess. After stirring for an hour at room temperature, the reaction mixture was poured into cold water. The aqueous solution was extracted with methylene chloride (10 ml x 3). Usual work-up as described in the earlier Jones oxidation furnished 0.16 g (90%) of diketone (56), which was crystallized from a benzene-petroleum ether mixture (60:40).

IR spectrum (KBr), ν_{max}: 1750 cm^{-1} (carbonyl).

The spectrum was superimposable to the diketone (56) obtained after photolysis.

11-Mesyloxypentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one Ethylene Ketal (90)

To a pyridine solution (5 ml) of the hydroxy-ketal (85, 0.5 g, 2.27 mmol) was added methanesulphonyl chloride (0.5 g, 4.36 mmol). The solution was kept at room temperature for 8 hr, when white needle-shaped crystals of pyridine hydrochloride formed. After reaction was complete (tlc), the solution was swirled and slowly added to an ice-cold solution of 30% hydrochloric acid (25 ml). The solution was extracted with methylene chloride (20 ml x 3). The organic phase was separated, washed once with dilute hydrochloric acid, then with saturated sodium bicarbonate solution and finally with brine. Evaporation of solvent gave a syrupy brownish liquid. Crystallization from ether-petroleum ether mixture gave white needle-shaped crystals

of the ketal-mesylate (90, 0.6 g, 88%), mp. 128-129°C.

IR spectrum (KBr), ν_{max}: 1345 and 1175 cm^{-1} (mesyloxy).

Lithium Aluminium Hydride Reduction of the Ketal-Mesylate (90)

The ketal-mesylate (90, 0.5 g, 1.68 mmol) was taken in anhydrous tetrahydrofuran (10 ml). The solution was added slowly to a slurry of lithium aluminium hydride (0.1 g, 2.63 mmol) in THF (5 ml). The reaction mixture was then refluxed for 4 hr. After cooling, LAH was cautiously decomposed by adding ice-cold 3% hydrochloric acid. The inorganic salts were filtered and washed with ether (10 ml x 3). The filtrate was extracted with addition of more ether (20 ml x 3). The ether layer was repeatedly washed with water (15 ml x 5), once with saturated sodium bicarbonate solution, and finally with brine. After drying, removal of solvent gave a pale yellow liquid (85, 0.32 g, 87%). It was distilled at 150°C/1 mm to give a colourless oil.

IR spectrum (neat), ν_{max}: 3650 (hydroxyl), 1130 cm^{-1} (ketal).

The spectrum was superimposable to the authentic hydroxy-ketal (85).

11-Hydroxypentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one(92)

Sodium borohydride (0.095 g, 2.5 mmol) was added to a 95% ethanolic solution (20 ml) of the once-sublimed dione (56, 1.74 g, 10 mmol). After 10 min. water (20 ml) was added and the mixture was refluxed for another 10 min. at 100°C. More water (25 ml)

was added, and the solution extracted with methylene chloride (50 ml x 3), washed with brine, dried and evaporated. The yellowish residue was taken up in benzene and chromatographed on silica-gel (40 g). Elution with 90% benzene and 10% ethyl acetate mixture gave traces of the starting material. Further elution with the same solvent and then with 80% benzene and 20% ethyl acetate mixture gave the ketol (92, 1.2 g, 68%). The ketol (92) afforded white needles when crystallized from a solution of benzene-petroleum ether (30:70), mp 270-271°C (lit.[79] 270-271°C).

IR spectrum (KBr), ν_{max}: 3350 (hydroxyl), 1740 (carbonyl), 1350, 1110, 1080, 1010 cm^{-1}.

PMR spectrum ($CDCl_3$): δ1.7 (2H, centre of AB quartet), 2.7 (ring CH, 8H, m), 4.15 (1H, br, s), 4.6 (1H, br, s).

^{13}CMR spectrum ($CDCl_3$): δ219.5(s), 119.4(s), 81.7(d), 72.2(d), 56.3(d), 55.0(d), 54.4(d), 50.0(d), 45.9(d), 45.3(?), 44.9(?), 44.8(?), 43.4(2C), 43.1, 42.2, 42.0, 41.7(2C), 40.7, 38.5(t), 37.0(d).

11-Mesyloxypentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one (94)

To a pyridine solution (10 ml) of the ketol (92, 3 g, 17.04 mmol) was added methanesulphonyl chloride (3 g, 26.20 mmol). The solution was kept at room temperature for 8 hr, when white needle-shaped crystals of pyridine hydrochloride formed. After reaction was complete (tlc), the solution was swirled and slowly

added to ice-cold solution of 30% hydrochloric acid (30 ml). The solution was extracted with methylene chloride (75 ml x 3). The organic phase was separated, washed once with dilute hydrochloric acid, then with saturated sodium bicarbonate solution, and finally with brine. After drying, evaporation of solvent gave a syrupy brownish liquid. It was crystallized from a solvent mixture of ether-benzene. White needle-shaped crystals were obtained (94, 3.8 g, 88%), mp 105-107°C.

IR spectrum (KBr), ν_{max}: 1750 (carbonyl), 1345 and 1175 cm^{-1} (mesyloxy).

PMR spectrum (DMSO-d_6): δ1.6 (2H, centre of AB quartet), 2.3-3.2 (C-H ring, 8H, m), 3.35 ($CH_3-\overset{O}{\overset{\|}{S}}(=O)-O-$, 3H, s), 4.7 (H-C-OMs, 1H, t, J = 4.5 Hz).

^{13}CMR spectrum ($CDCl_3$): δ214.9(s), 78.1(d), 51.2(d), 49.9(d), 44.2(d), 42.1(2C, d), 40.7(d), 40.5(d), 38.4(q), 38.3(t), 37.0(d).

Lithium Aluminium Hydride Reduction of 11-Mesyloxypentacyclo-[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one (94)

The keto-mesylate (94, 5 g, 19.68 mmol) was dissolved in anhydrous tetrahydrofuran (50 ml). The solution was added slowly to a slurry of lithium aluminium hydride (1 g, 26.32 mmol) in THF (10 ml). The reaction mixture was then refluxed for 6 hr. The mixture was cooled in an ice-bath and the LAH cautiously decomposed by dropwise addition of cold 30% hydrochloric acid. All the inorganic salts slowly dissolved. The solution was

extracted with ether (50 ml x 3). The ether layer was repeatedly washed with water (20 ml x 5), one with saturated sodium bicarbonate solution and finally with brine. After drying, removal of solvent gave a white solid which gave two clear spots on the tlc plate (solvent: 95% benzene; 5% ethyl acetate). The solid was taken up in a solution of benzene-petroleum ether and charged on a silica-gel column (80 g). Slow elution with 70% benzene and 30% petroleum ether mixture gave the oxa-bird-cage ether, 4-oxahexacyclo[5.4.1.$O^{2,6}$.$O^{3,10}$.$O^{5,9}$.$O^{8,10}$]dodecane (95) as a white solid (2.6 g, 83%). It was sublimed twice at 80°C/ 20 mm giving a waxy solid, mp 228-229°C (lit.[74] 228-230°C).

IR spectrum (KBr), ν_{max}: 2963, 2862, 1325, 1025, 965, 925, 910 and 865 cm^{-1}.

PMR spectrum ($CDCl_3$): δ1.7 (2H, centre of AB quartet, J=11 Hz) 2.2 - 3.0 (8H, m), 4.73 (2H, s).

^{13}CMR spectrum ($CDCl_3$): δ85.8(d), 54.5(d), 44.0(d), 43.9(t), 43.7(d), 41.6(d).

Further elution with 70% benzene and 30% petroleum ether mixture, and then with benzene gave an inseparable mixture of pentacyclo[5.4.0.0^{2,6}.$O^{3,10}$.$O^{5,9}$]undecan-8-ol (96), and tetracyclo[6.3.0.$O^{4,11}$.$O^{5,9}$]undecan-2-ol (97) as a white solid. The solid crystallized from hexane solution giving fine needle-like white crystals of 96 and 97 (0.2 g, 6%), mp 207-208°C).

IR spectrum (KBr), ν_{max}: 3460 (hydroxyl), 2960, 2875, 1460, 1360, 1080 cm^{-1}.

PMR spectrum ($CDCl_3$): δ0.9-1.38 (4H, m), 1.45-1.88 (4H, m), 2.13-2.88 (ring C<u>H</u>, 18H, m), 3.96 (1H, br, s), 4.34 (1H, m).

^{13}CMR spectrum ($CDCl_3$): δ78.5, 77.1, 75.6, 74.3, 73.9, 50.5, 50.3, 47.0, 46.2, 45.8, 44.0, 43.1, 42.3, 42.0, 40.0, 39.6, 38.8, 38.3, 36.3, 36.0, 35.1, 32.2.

Jones Oxidation of the Mixture of Alcohols 96 and 97

To a cold stirred solution of the mixture of alcohols 96 and 97 (0.15 g) in acetone (5 ml) was added dropwise Jones reagent, till in excess. After allowing the reaction mixture to stir for an hr, it was poured into cold water. The aqueous solution was extracted with ether (15 ml x 3), washed with saturated sodium carbonate solution and with brine (20 ml x 2). Drying and removal of solvent furnished a white solid, a mixture of 98 and 99. Sublimation of the solid at 140°C/20 mm yielded 0.12 g (81%) of a waxy solid, mp 160-161°C.

IR spectrum (CCl_4), ν_{max}: 2995, 2888, 1750 cm^{-1} (carbonyl).

PMR spectrum ($CDCl_3$): δ1.4-3.25 (C<u>H</u> & C<u>H</u>$_2$, en).

^{13}CMR spectrum ($CDCl_3$): δ221.1(s), 220.4(s), 56.7(d), 53.1(?), 51.9(d), 50.3(?), 48.7(d), 48.5, 47.5(d), 47.4(d), 46.8(t), 44.6, 43.9(t), 43.4(?), 42.8(d), 41.7(d), 41.1(t), 39.6(d), 37.7(t), 36.9(d), 31.2(t).

Alane Reduction of the Oxa-bird-cage Ether (95)

A slurry of lithium aluminium hydride (1.2 g, 31.58 mmol) was made in anhydrous ether (20 ml). To the ice-cold slurry

a solution of the oxa-bird-cage ether (95, 1 g, 6.25 mmol) in anhydrous ether (10 ml) was added dropwise. To this, anhydrous aluminium chloride (1.4 g, 10.48 mmol) was added in small pinches, carefully. After complete addition, ether was gently refluxed for 16 hr. The mixture was then cooled in an ice-bath and the LAH-$AlCl_3$ mixture was cautiously decomposed by adding dropwise moist ether. The inorganic salts were dissolved by pouring cold 30% hydrochloric acid into the reaction flask. The clear solution was extracted by addition of more ether (50 mlx3). The organic layer was washed with brine and dried. Removal of solvent gave a white solid which was a mixture of the starting material (95), and the inseparable alcohols (tlc) 96 and 97. A solution of the solid in benzene-petroleum ether was charged on a silica-gel column (30 g). Slow elution with 70% benzene and 30% petroleum ether mixture gave the unreacted oxa-bird-cage ether (95, 0.7 g, 70%). Sublimation of the solid at 80°C/20 mm gave a waxy solid, mp 228-229°C (lit.[74] 228-230°C).

IR spectrum (KBr), ν_{max}: 2963, 2862, 1325, 1025, 965, 925, 910, 865 cm^{-1}.

Further elution with 70% benzene and 30% petroleum ether mixture, and then with benzene gave an inseparable mixture of the two alcohols 96 and 97. The solid obtained on evaporation of solvent yielded on crystallization from hexane solution fine needle-like white crystals of 96 and 97 (0.2 g, 20%), mp 207-208°C.

IR spectrum (KBr), ν_{max}: 3460 (hydroxyl), 2960, 2875, 1460, 1360 and 1080 cm^{-1}.

Rearrangement of the Oxa-bird-cage Ether (95) in Methanesulphonic Acid to 4-Mesyloxypentacyclo[6.3.0.^{2,6}.0^{3,10}.0^{5,9}]undecan-7-ol(101)

To a stirred solution of the oxa-bird-cage ether (95, 1 g, 6.25 mmol) in anhydrous methylene chloride (15 ml) was added anhydrous methanesulphonic acid (5 g, 52.08 mmol). Stirring was continued for 8 hr at room temperature. The reaction mixture was then carefully poured into ice-cold sodium bicarbonate solution. The solution was extracted by adding more methylene chloride (15 ml x 3). The organic phase was successively washed with saturated sodium bicarbonate solution and brine. After drying, removal of solvent furnished the hydroxy-mesylate (101) as a brownish syrupy liquid (1.5 g, 94%).

IR spectrum (neat), ν_{max}: 3400, 2988, 1355, 1190 cm^{-1}.

PMR spectrum (100.1 MHz, $CDCl_3$): δ1.4 (-C<u>H</u>$_2$, 2H, q), 1.97-2.6 (C<u>H</u> ring, 8H, en), 2.72(C<u>H</u>-O<u>H</u>, 1H, s), 3.05 (-O-$\overset{O}{\underset{O}{S}}$-C<u>H</u>$_3$, 3H, s), 4.15 (C<u>H</u>-OH, 1H, s), 4.85 (MsO-C<u>H</u>, 1H, s).

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diol (100)

A solution of the diketone (56, 10 g, 57.47 mmol) in anhydrous tetrahydrofuran (40 ml) was added to a magnetically stirred slurry of lithium aluminium hydride (3 g, 78·94 mmol) in anhydrous tetrahydrofuran (20 ml). After addition had been completed the reaction mixture was refluxed for 10 hr. The mixture was cooled in an ice-bath and cautiously decomposed by addition of water (4 ml) followed by addition of sufficient 33% sulphuric acid until inorganic salts had dissolved. The organic

layer was separated, the aqueous portion extracted with methylene chloride (100 ml x 3) and the combined organic extracts washed with water (50 ml x 5) and dried. Removal of methylene chloride yielded 9.2 g (90%) of the diol (100). It was crystallized from a solution of ether containing a few ml of methylene chloride, mp 274°C (lit.[79] 273.5°C).

IR spectrum (KBr), ν_{max}: 3200 cm^{-1} (br, hydroxyl).

PMR spectrum (100.1 MHz, $CDCl_3$): δ1.35 (2H, centre of AB quartet, J = 10 Hz), 2.15 - 2.8 (8H, br, d), 3.75 (2H, s), 6.35(2H,s).

Rearrangement of Pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-diol (100) to 4-Mesyloxypentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-7-ol (101)

To a stirred solution of the diol (100, 5 g, 28.08 mmol) in dry chloroform (20 ml) was added anhydrous methanesulphonic acid (20 g, 208.3 mmol). The reaction mixture was refluxed for 10 hr. After cooling, it was poured into ice-cold sodium bicarbonate solution. The aqueous layer was extracted with chloroform (150 ml x 3), washed with brine, and dried. Removal of solvent furnished 101 as a brownish syrupy liquid, yielding 7.1 g.(99%). HPLC analysis of 101 using μ-Porasil column (methanol eluent) and a refractive index detector showed two peaks (time 2.5, 2.7 min, ratio 49:3). The hydroxymesylate (101) was not further purified but had the expected spectral features.

IR spectrum (neat), ν_{max}: 3400 (hydroxyl), 2998, 2988, 1355, and 1190 cm^{-1} (mesyloxy).

PMR spectrum (100.1 MHz, $CDCl_3$): δ1.4 ($-C\underline{H}_2-$, 2H, q), 1.97 - 2.6 (C<u>H</u> ring, 8H, en), 2.72 (-CH-O<u>H</u>, 1H, s), 3.05 ($-O-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-C\underline{H}_3$, 3H, s), 4.15 (-C<u>H</u>-OH, 1H, s), 4.85 (MsO-C<u>H</u>-, 1H, s).

4-Mesyloxypentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-7-one (<u>104</u>)

To a cold stirred solution of the hydroxy-mesylate(<u>101</u>) (7.1 g, 27.73 mmol) in acetone was added dropwise Jones reagent, till in excess. After allowing the reaction mixture to stir for 4 hr at room temperature, it was poured into cold water. The aqueous solution was extracted with ether (125 ml x 3), washed with sodium bicarbonate solution (100 ml) and twice with brine solution (150 ml x 2), and dried. Removal of solvent furnished a light yellow viscous oil; yield, 6.9 g (98%). The oil solidified on storage in a refrigerator and part of the solid was sublimed (100°C/1 mm) to give a white waxy solid <u>104</u>, mp 58-59°C.

<u>Anal</u>. for $C_{12}SO_4H_{14}$: Calcd C, 56.69; H, 5.51.
(M.W. 254) Found C, 55.98; H, 4.98

IR spectrum (KBr), ν_{max}: 2998, 2988, 1760 (carbonyl), 1355 and 1190 cm^{-1} (mesyloxy).

PMR spectrum (100.1 MHz, $CDCl_3$): δ1.7 ($-C\underline{H}_2$, 2H, s), 1.97 (C<u>H</u>, 2H, s), 2.2-2.8 (C<u>H</u> ring, 5H, en), 3.05 ($O-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-C\underline{H}_3$, 3H, s), 4.85 (MsO-C<u>H</u>, 1H, s).

4-(D_3)-Trishomocubanol(4-Pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]-undecanol) (<u>105</u>)

To the keto-mesylate(<u>104</u>, 6.9 g, 27 mmol) was added ethylene glycol (15 ml) and hydrazine hydrate (99-100%, 6g, 120 mmol).

The reaction mixture was heated to 90-100°C and was kept stirring for 1.5 hr at this temperature. After cooling, solid potassium hydroxide (6 g, 107 mmol) was added and temperature slowly raised to 190-195°C and maintained at a gentle reflux for 5 hr. After cooling, the solution was poured into ice-cold 30% hydrochloric acid (150 ml) and extracted with ether (150 ml x 4). The organic layer was washed with sodium bicarbonate solution and then with brine. Removal of solvent gave a white solid residue. Crystallization of the residual solid from hexane yielded 3.1 g (71%) of 4-(D_3)-trishomocubanol (105); mp 165-166°C (lit.[66,77] 168.5° and 170°C).

IR spectrum (KBr), ν_{max}: 3300 (hydroxyl), 2965, 2875, 1460, 1350, 1300, 1075 cm^{-1}.

PMR spectrum (CCl_4): δ1.25-1.5 (4H, br, m), 1.8-2.38 (8H, br, m), 2.65 (1H, br, m), 4.1 (1H, s).

(D_3)-Trishomocubanone (4-Pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecanone) (51)

Jones reagent was added dropwise to a solution of 4-(D_3)-trishomocubanol (105, 3.1 g, 18 mmol) in acetone (35 ml), till the yellow colour persisted. Stirring was continued for 4 hr. The reaction mixture was poured into ice-cold water and extracted with ether (100 ml x 3). The ethereal solution was washed with aqueous sodium carbonate solution (50 ml x 2), with brine, and dried. On evaporation of solvent, a white solid was obtained.

Sublimation at 90°C/8 mm yielded 3.0 g (98%) of (D_3)-trishomocubanone (51); mp 160-161°C (lit.[66,77] 160° and 163°C).

IR spectrum (nujol), ν_{max}: 2960, 2870, 1770 and 1750 (carbonyl), 1465, 1290, 1280, 1220, 1160, 890 cm^{-1}.

PMR spectrum (CCl_4): δ1.5 (2H), 1.6 (2H), 1.8 (2H), 2.4(6H).

Pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-4,7-diol (103)

A solution of the hydroxy-mesylate (101, 1.3 g, 5.08 mmol) in anhydrous tetrahydrofuran (5 ml) was added to a magnetically stirred slurry of lithium aluminium hydride (0.7 g, 18.42 mmol) in 10 ml of anhydrous tetrahydrofuran. After addition was complete, the reaction mixture was refluxed for 6 hr. The mixture was cooled in an ice-bath, cautiously decomposed by addition of sufficient 33% hydrochloric acid until inorganic salts had dissolved. The aqueous solution was extracted with warm (50°C) ethyl acetate (50 ml x 5) and the combined organic extracts washed with water and dried. Removal of solvent gave 0.55 g (61%) of the diol (103) as white flakes; mp 203-204°C (lit.[74] 203-205°C).

IR spectrum (KBr), ν_{max}: 3280 (hydroxyl), 2960, 2895, 2875, 1350, 1275, 1190, 1100, 1075, 1065 and 775 cm^{-1}.

PMR spectrum (100.1 MHz, DMSO-d_6): δ1.28 (2H, cente of AB quartet, J = 10 Hz), 1.66-2.7 (8H, m), 3.92 (H-C-OH, 2H, d), 4.2 (-C-OH, 2H, br, s).

Pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-4,7-dione (64)

To a stirred solution of the diol (103) (0.55 g, 3.09 mmol) in 50% v/v aqueous acetone (10 ml) of 0°C was added Jones reagent dropwise till in excess. After the addition was complete, the reaction mixture was stirred for 5 hr at room temperature. Water was added to dissolve the chromium salts and the mixture was extracted with ether (50 ml x 3). The organic layer was washed with saturated sodium bicarbonate solution with brine, and dried. Removal of solvent afforded 0.50 g (93%) of the dione (64). It was crystallized from a solution of hexane, mp 213-216°C (lit.[74] 213-214°C).

IR spectrum (KBr), ν_{max}: 3020, 2975, 1785 and 1765(carbonyl), 1150 cm^{-1}.

PMR spectrum ($CDCl_3$): δ1.75 (2H, s), 2.19 (4H, br, s), 2.85 (4H, br, s).

Tetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undecane-2,6-dione (78)

A mixture of the diketone (56, 2.0 g, 11.49 mmol) and zinc (5 g, 76.48 mmol), glacial acetic acid (100 ml) was stirred at room temperature for 5 hr. It was poured into ice-water and extracted with methylene chloride (75 ml x 3). The organic layer was washed with dilute sodium hydroxide solution (50 ml x 2). After drying, removal of solvent gave 1.9 g, 94% of the tetracyclic dione (78) as a white solid. It was crystallized from a solution of benzene to give colourless sugar shaped crystals; mp 255°C (lit.[87] 255°C).

IR spectrum (KBr), ν_{max}: 1750 cm^{-1} (carbonyl).

PMR spectrum ($CDCl_3$): δ1.8-2·0(-C<u>H</u>$_2$, 2H, m), 2.1-2.3 (C<u>H</u>, 4H, br, s), 2.6-2.8 (C<u>H</u>$_2$-C(=O)-, 4H, br, s), 2.7-2.9 (C<u>H</u>-C(=O)-, 2H, m).

2-Hydroxy-2,7-oxa-tetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undecane (<u>107</u>)

To a solution of tetracyclic diketone (<u>78</u>, 1.5 g, 8.5 mmol) in distilled ethanol (20 ml) was added sodium borohydride (0.1 g, 2·63 mmol). The solution was stirred for 6 hr. The sodium borohydride was decomposed by adding cold 10% hydrochloric acid (10 ml) and the solution extracted with ether (25 ml x 3). The organic phase was washed with aqueous sodium bicarbonate solution, with brine, and dried. Removal of solvent gave the lactol (<u>107</u>) in 1.4 g yield (92%). The lactol was crystallized from a solution of hexane; mp 223°C (lit.[72] 223-223.5°C).

IR spectrum (KBr), ν_{max}: 3500 (hydroxyl), 2995, 1295, 1245, 1095 and 1045 cm^{-1}.

PMR spectrum ($CDCl_3$): δ1.56-2.61 (11H, m), 2.82 (1H, br, s), 4.63 (O-C-<u>H</u>, 1H, t, J = 7 Hz), 4.89 (-C-O<u>H</u>, 1H, s).

^{13}CMR spectrum ($CDCl_3$): δ115.7(s), 81.1(d), 58.7(d), 53.9(d), 49.4(d), 47.6(d), 43.7(t), 42.3(d), 41.4(d), 38.1(t), 37.9(t).

2-Mesyloxy-2,7-oxa-tetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undecane (<u>109</u>)

To a cold pyridine solution (20 ml) of the lactol (<u>107</u>, 1.4 g, 7.87 mmol) was added methanesulphonyl chloride (1.75 g, 15.28 mmol). The solution was kept at room temperature for 6 hr,

when white needle-shaped crystals of pyridine hydrochloride formed. After reaction was complete, the solution was swirled and slowly added to an ice-cold solution of 30% hydrochloric acid. After pyridine was neutralized, the solution was extracted with methylene chloride (25 ml x 3). The methylene chloride layer was separated, washed once more with cold dilute hydrochloric acid, then with saturated sodium bicarbonate solution, and finally with brine. After drying, evaporation of solvent gave a deep-brown viscous liquid. Crystallization from a ether-hexane mixture gave white needle-shaped crystals of the mesylate (109, 1.85 g, 92%); mp 58-59°C.

IR spectrum (KBr), ν_{max}: 2995, 2885, 1360 and 1175 cm^{-1} (mesyloxy).

PMR spectrum ($CDCl_3$): δ1.64-20 (4H, m), 2.16-2.39 (5H, m), 2.5 (1H, br, s), 3.0 (2H, br, s), 3.13 ($\underline{CH_3}$-$\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}$-O, 3H, s), 4.78 (O-C-$\underline{H}$, 1H, t, J= 5 Hz).

^{13}CMR spectrum ($CDCl_3$): δ122.3 (s), 83.1(s), 57.9(d), 52.8(d), 49.2(d), 46.8(d), 44.3(t), 42.0(d), 41.5(d), 40.5(d & q), 38.0(t), 37.7(t).

Reaction of the Mesylate (109) with Potassium-t-butoxide

To a solution of the mesylate (109, 0.15 g, 0.59 mmol) in anhydrous dimethyl sulphoxide (4 ml) was added freshly sublimed potassium-t-butoxide (0.25 g, 2.23 mmol). The solution was warmed to 70°C and ketp stirring for an hour. The solution was

cooled, poured into water (10 ml), and extracted with ether (15 ml x 3). The ether layer was repeatedly washed with water (10 ml x 5) and then with brine. After drying, evaporation of solvent yielded to lactol (107, 0.09 g, 86%). Crystallization from hexane gave a white fluffy solid; mp 223°C, (lit.[72] 223-223.5°C).

IR spectrum (KBr), ν_{max}: 3500 (hydroxyl), 2995, 1295, 1245, 1095 and 1045 cm^{-1}.

2-Phenyl-2,7-oxa-tetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undecane (111)

The lactol (107, 0.9 g, 5.06 mmol) was dissolved in dry benzene (20 ml) and concentrated sulphuric acid (0.5 ml, 99.9%) was added. The solution was refluxed for an hour. After cooling the reaction mixture more benzene was added. The benzene solution was washed with water, saturated sodium bicarbonate solution and finally with brine. After evaporation of solvent the phenyl ether (111) was obtained as a white solid (1.1 g, 92%). It was crystallized from a cold solution of petroleum ether; mp 108-109°C.

Mass spectrum (m/e): 238(M^+), 105($C_8H_9^+$), 91($C_7H_7^+$).

IR spectrum (KBr), ν_{max}: 3050, 1055, 745 and 710 cm^{-1} (aromatic).

PMR spectrum (90 MHz, CCl_4): δ0.8-3.1 (CH ring, 12H, en), 4.75 (-O-C-H, 1H, t, J= 5 Hz), 7.0-7.5 (aromatic H, 5H, m).

^{13}CMR spectrum ($CDCl_3$): δ 146.8(s), 128.0(d), 126.2(d), 124.7(d), 93.9(s), 83.4(d), 62.4(d), 55.5(d), 49.8(d), 49.0(d), 48.1(t), 43.1(d), 42.2(d), 39.0(t), 38.1(t).

2-Naphthyl-2,7oxa-tetracyclo[6.3.0.$o^{4,11}$.$o^{5,9}$]undecane (112)

The lactol (107, 0.1 g, 0.56 mmol) and naphthalene (1 g, 7.8 mmol) were dissolved in carbon tetrachloride (8 ml). Concentrated sulphuric acid (0.1 ml, 99.9%) was added. The solution was refluxed for 5 hr. After cooling, more carbon tetrachloride was added and the solution was washed with water, saturated sodium bicarbonate solution and brine. After evaporation, the solid obtained was taken up in petroleum ether and charged on a silica-gel column (10 g). Elution with petroleum ether gave the unreacted naphthalene. Further elution with 50% petroleum ether and 50% benzene mixture afforded the two products α- and β-substituted naphthalene (112). They were inseparable on the column. Solvent evaporation yielded 0.08 g (52%) of a viscous oil. It was crystallized from chilled hexane solution to give a white fluffy solid of 112; mp 102°C.

Anal. for $C_{21}H_{10}O$: Calcd C, 92.65; H, 7.35.
(M.W. 272) Found C, 92.50; H, 7.10.

IR spectrum (KBr), ν_{max}: 3050, 1055, 775 cm^{-1} (aromatic).

PMR spectrum (90 MHz, CCl_4): δ0.8-3.1 (CH ring, 12H, en), 4.78 (O-C-H, 1H, t, J = 7 Hz), 7.15-8.7 (aromatic H, 7H, m).

Dimerization of 11-Hydroxypentacyclo[5.4.0.0^{2,6}.$o^{3,10}$.$o^{5,9}$]-undecan-8-one (92) to give (118)

The hydroxy-ketone (92, 0.45 g, 2.56 mmol) was dissolved in dry benzene (10 ml). After adding a drop of concentrated

sulphuric acid (99.9%), the solution was refluxed for an hour. After cooling, more benzene was added, and the solution was washed with water, dilute sodium bicarbonate solution and with brine. After drying, a brown syrupy liquid (0.4 g, 89%) remained after solvent evaporation. The liquid was dissolved in a small amount of benzene and charged on a silica-gel column (10 g). Elution with a mixture of 90% benzene and 10% ethyl acetate mixture gave a clean white solid on solvent removal. A hexane solution afforded beautiful star-like crystals of the dimer 118; mp 202-203°C.

Anal. for $C_{22}H_{22}O_3$: Calcd C, 79.01; H, 6.60.
(M.W. 334) Found C, 78.95; H, 6.38.

Mass spectrum (m/e): 334 (M^+), 159 ($C_{11}H_{11}O^+$).

IR spectrum (KBr), ν_{max}: 3050 (hydroxyl), 1750 (carbonyl), 1335 cm^{-1}.

PMR spectrum (90 MHz, CCl_4): δ0.9-3.2 (20H, m), 3.95(O-C<u>H</u>-, 1H, t, J = 4 Hz), 4.52 (O-C<u>H</u>-, 1H, t, J = 5.5 Hz).

^{13}CMR spectrum ($CDCl_3$): δ215.8(s), 122.1(s), 81.5(d), 75.3(d), 54.6(d), 53.7(2C), 52.6(d), 50.2(d), 45.2(d), 44.4(?), 44.2(?), 43.5(?), 42.9(?), 42.0(?), 41.7(2C, d?), 40.9(d), 38.4(t), 37.0(d).

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CHAPTER II

NOVEL C_{10}-CARBOCYCLES FROM PENTACYCLO[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]UNDECANE-8,11-DIONE VIA SCHMIDT FRAGMENTATION

II.1 Abstract

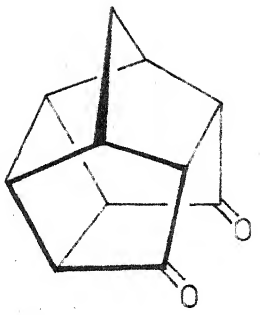
A novel one step rearrangement of pentacyclo-[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione (1) to tetracyclo-[4.3.1.$0^{2,9}$.$0^{4,8}$]decane (18) and 3,7-ethano-tricyclo[3.3.0.$0^{3,7}$]-octane (19) ring system is reported. Reaction of dione (1) with sodium azide in methanesulphonic acid furnished two crystalline mesylates which have been assigned structures 20 and 21 on the basis of complementary spectral data (^{1}H NMR, ^{13}C NMR and IR) as well as few selected chemical reactions. The structures of 20 and 21 have been unambiguously verified by X-ray crystal structure determination. The close relationship between 20 and 21 and their common genesis has been established through a facile conversion of 20 into 21 via solvolysis in methanesulphonic acid.

An interesting photochemical oxa-di-π-methane rearrangement of the β,γ-unsaturated ketone 21 to the tetracycle 28 is also reported. A plausible mechanism for the formation of 20 and 21 from 1 under Schmidt reaction conditions is proposed.

II.2 Introduction

The pentacyclic dione (1), readily obtainable[1] via the intramolecular $\pi_s^2 + \pi_s^2$ photocycloaddition of the cyclopentadiene-p-benzoquinone Diels-Alder adduct, is endowed with structural features that make it an attractive target for the study of new skeletal reorganizations. Several research groups around the world have carried out a variety of interesting synthetic manouvres, employing 1 as the substrate.[2-15] In the first chapter of this thesis we have described several reactions of the ring system 1 and, in particular, the generation of a carbonium ion intermediate of the type 2, which ultimately rearranged to 3, bearing the trishomocubyl framework (Scheme II.1). Our continued fascination with the system 1 and the stimuli provided by some interesting results with closely related systems in our laboratory[16-18] prompted us to explore the fate of cyclobutyl carbonium ion 4 derived from 1 as a source of new rearrangements of this system.

For some time now, our group has been interested[16-18] in the study of rearrangements of cyclobutyl carbonium ions[19]



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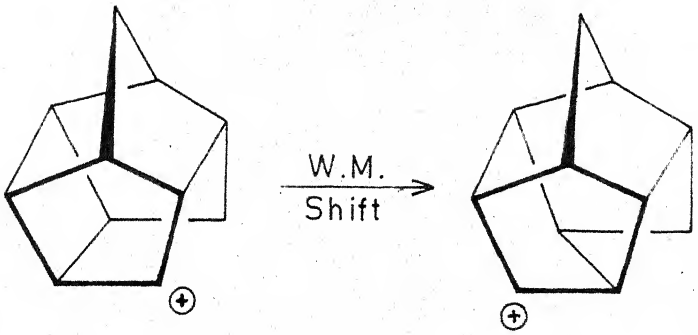
Scheme II.1



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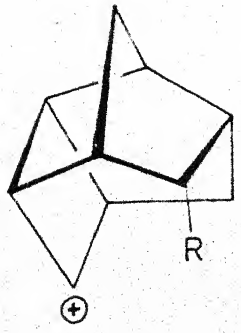

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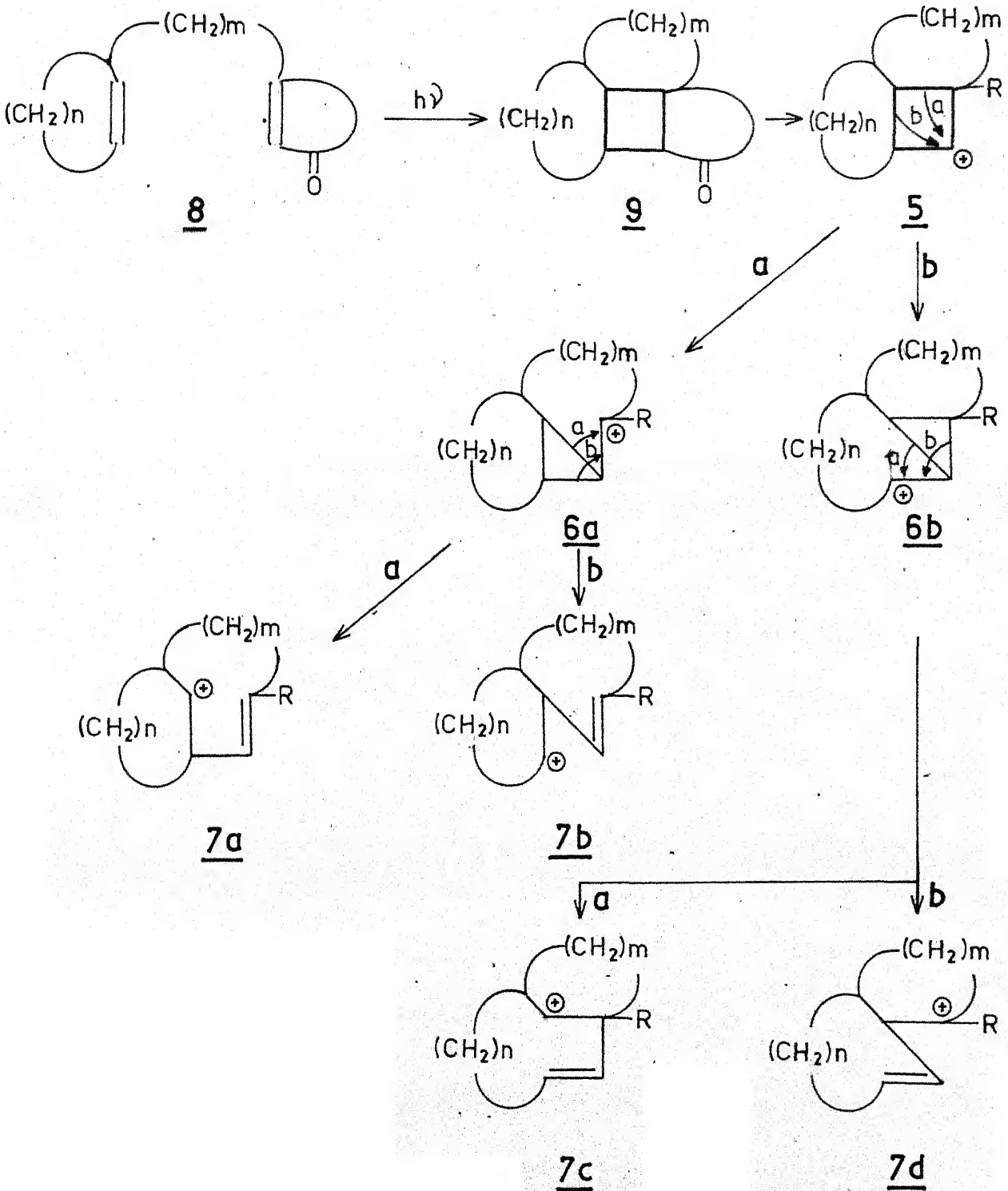
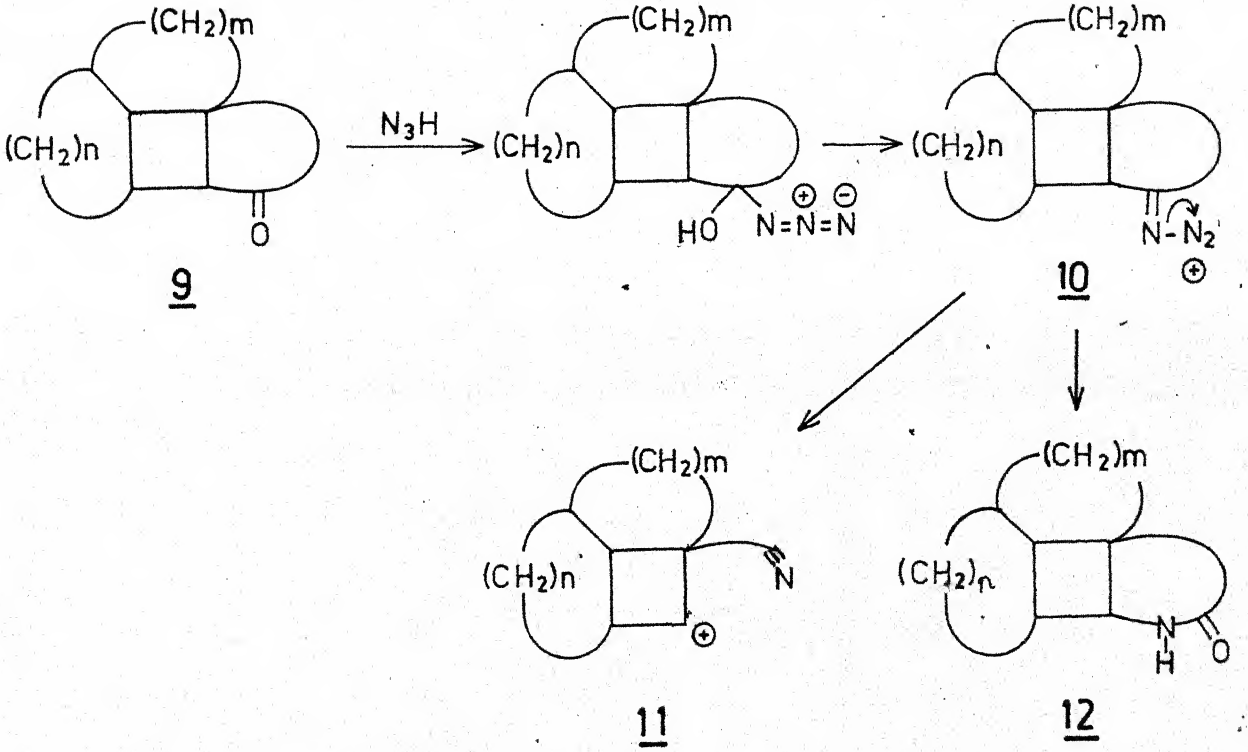
constrained within diverse polycyclic networks. One of the objects of this study has been the expectation that fused cyclobutyl carbonium ions like 5 might rearrange to cyclopropylcarbinyl carbonium ions 6a,b and/or homoallylic carbonium ions 7a,b,c,d, thus providing ready access to new and homologated carbocyclic frameworks (Scheme II.2). This offers an attractive synthetic strategy to a variety of polycycles, considering the fact that polycyclic cyclobutyl ketones, like 9, can be rendered available quite easily through intramolecular $\pi_s^2 + \pi_s^2$ photocycloaddition (Scheme II.2), and that they in turn can serve as facile precursors of cyclobutyl carbonium ions (Scheme II.3). Among the various reactions by which the cyclobutylketones 9 can be fragmented to the cyclobutyl carbonium ions 5, the Schmidt fragmentation is obviously the reaction of choice (see Scheme II.3). Since, the formation of carbonium ion 11 from Schmidt intermediate 10 involves substantial strain release within the polycyclic framework, it ensures the ascendancy of the fragmentation process (10 → 11) over the more often encountered rearrangement (10 → 12) leading to lactam formation.

Another aspect of the rearrangement of the cyclobutyl carbonium ion, e.g. 5, that interested and initiated us to its exploration was the stereo-electronic control of cyclobutyl ⇌ cyclopropylcarbinyl ⇌ homoallylic carbonium ion rearrangements. In the fused polycyclic systems, the various carbonium ions will have different and discrete geometries and alignment

Scheme II.2



Scheme II.3



of neighbouring bonds depending upon the size and shape of the carbocyclic framework.

Some of the interesting rearrangements of strained polycyclic ketones observed by us[16-18] under Schmidt reaction conditions are enumerated in Scheme II.4. In the case of all the ketones 13, 14, 15 and 16 mentioned in the Scheme, exclusive and regiospecific fragmentation occurred (as revealed by the appearance of cyano functionality) and the cyclobutyl carbonium ion intermediate was produced.* Further rearrangements of this carbonium ion led to the formation of observed products. Since, the Schmidt fragmentation in all the cases reported here was carried out in the nucleophilic medium of methanesulphonic acid (MsOH), the rearranged carbonium ions were trapped as the mesylate derivatives. A representative mechanism for the formation of brendane derivative 17 from 1,3-bishomocubanone 13 which involves the cyclobutyl → cyclopropylcarbinyl → homoallylic carbonium ion type rearrangement is depicted in Scheme III.5.

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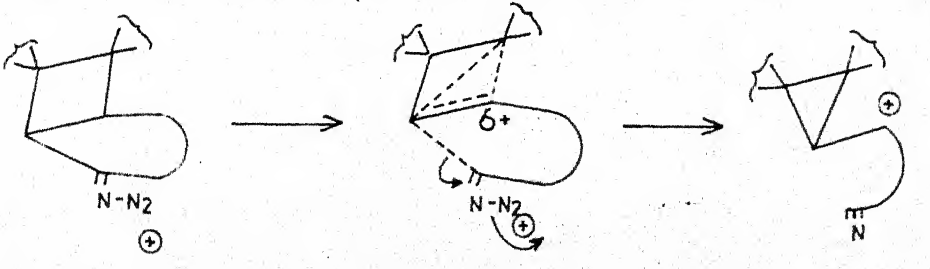
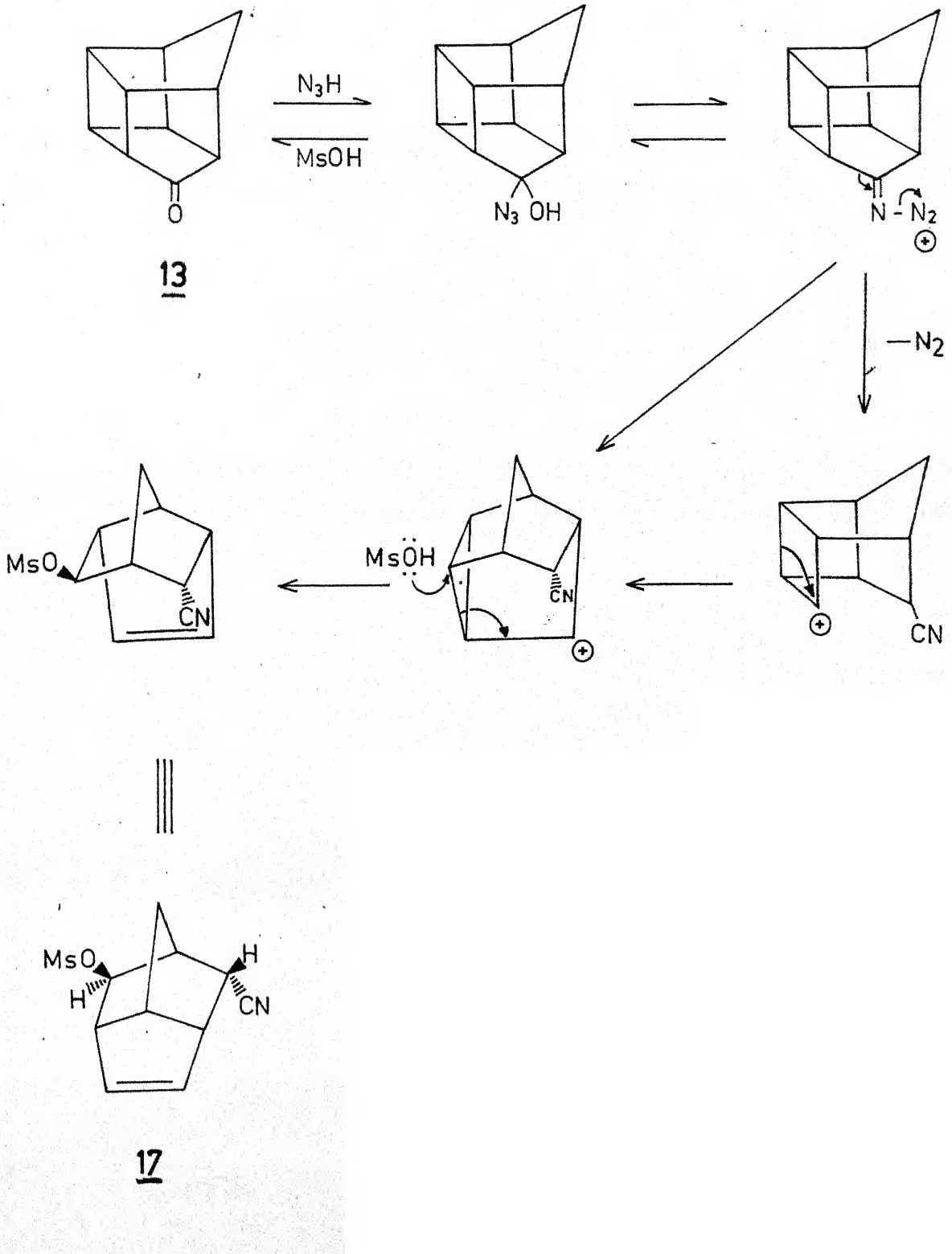
*The existence of a discrete cyclobutyl carbonium ion intermediate in all the cases is neither necessary nor certain. It is possible that in some cases the C-C bond scission might proceed with participation by one of the suitably disposed strained σ bond during the Schmidt fragmentation.



Scheme II.5



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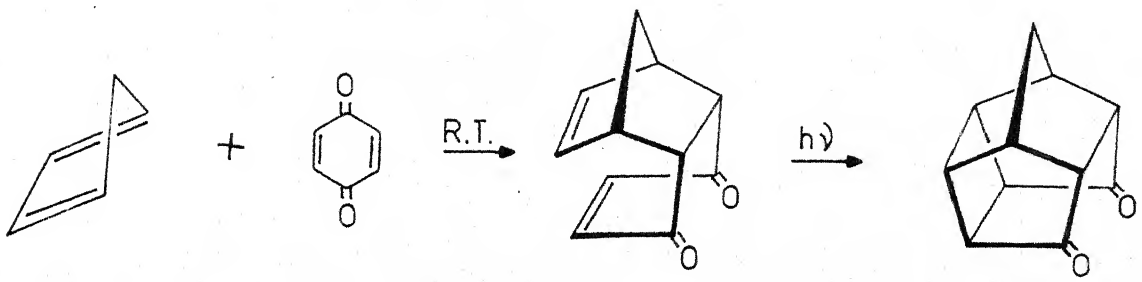
In the light of these rearrangements, it was of obvious interest to study the fate of cyclobutyl carbonium ion 4 derived from the pentacyclic dione (1), as indicated earlier. The pentacyclic dione (1) is readily synthesized according to Scheme II.6.

In this chapter of the thesis we describe the formation and structure elucidation of two novel C_{10} carbocyclic systems 18 and 19 from 1 under Schmidt reaction conditions.

II.3 Results and Discussion

Reaction of pentacyclic dione (1) with sodium azide (one equivalent) in methanesulphonic acid (2 hr, 0-5°C) and usual work-up (vide experimental) furnished a complex mixture of products. Column chromatography on silica-gel resulted in the isolation of two crystalline mesylates 20, mp 179°C and 21, mp 171°C, in 15 and 10% yield respectively (Scheme II.7). It was also observed that the relative yields of 20 and 21 were markedly dependent on the reaction time. Prolonged reaction time resulted in the depletion of 20 and enrichment of 21. In a separate experiment, it was shown mesylate 20 in methanesulphonic acid was quantitatively transformed to 21, thus revealing the intimate structural relationship between the two mesylates. The stereo-structures of these rearranged mesylates were elucidated with the aid of ^{13}C NMR spectroscopy, high-

Scheme II.6



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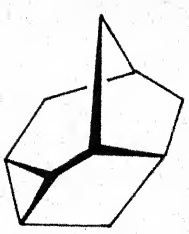

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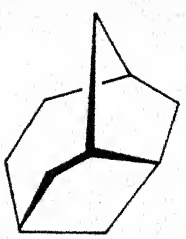

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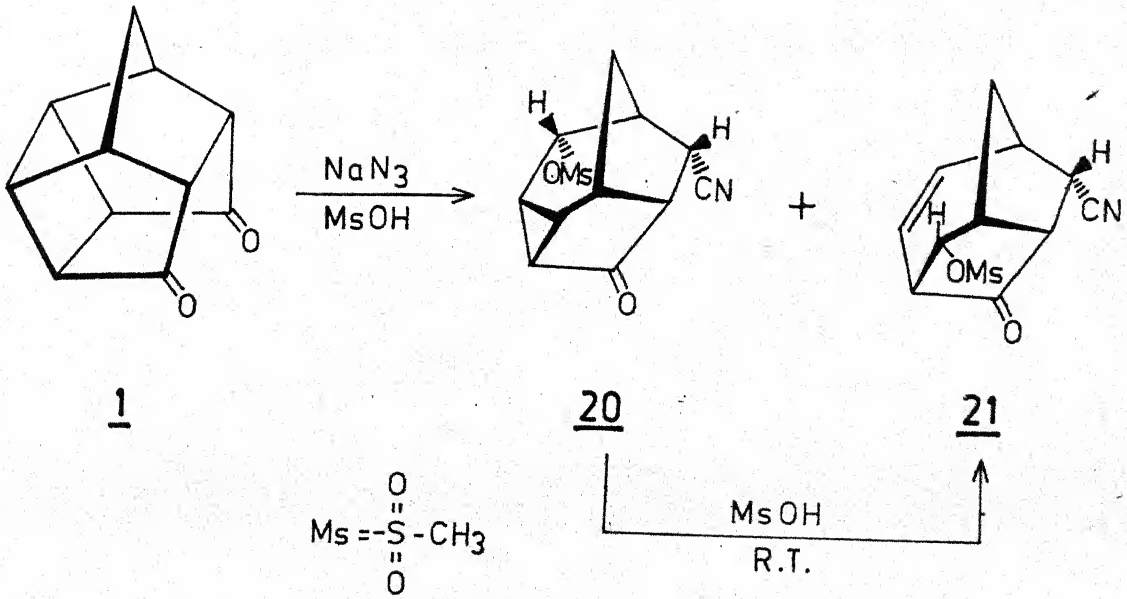
Scheme II.7



resolution ^{1}H NMR spectroscopy in conjunction with double-resonance experiments, and chemical transformations. Further unambiguous proof for structures 20 and 21 was derived through X-ray crystal structure determination.* We summarize below the complementary spectroscopic evidence that led to the formulations 20 and 21 for the two mesylates obtained from 1.

The more polar of the two mesylates 20, mp 179°C, analysed correctly for $C_{12}H_{13}NO_4S$ and showed in its mass spectrum the highest mass peak at M^+ 267, which is consistent with its molecular formula. The IR spectrum (Fig. II.1) was quite informative and revealed the nature of the functional groups. Thus, the presence of a cyano group (2275 cm^{-1}) and a sulphonate ester group (1340 and 1175 cm^{-1}) was clearly indicated by diagnostic IR bands.[20] Furthermore, the carbonyl absorption at 1725 cm^{-1} was indicative of being either in a six-membered ring or in a five membered ring in conjugation with a double bond or a cyclopropane ring. The ^{1}H NMR spectrum (Fig. II.2)(60 MHz, DMSO-d_6) confirmed the presence of a sulphonate ester functionality and exhibited signals at δ 3.20 (3H, s) and 5.6 (1H, t,

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*The crystal structures of mesylates 20 and 21 were investigated employing X-ray diffraction techniques in collaboration with Professor K. Venkatesan, Indian Institute of Science, Bangalore. Structural details like bond lengths and bond angles for 20 are available and have been included here. Preliminary findings on 21 are in agreement with the assigned structure. Further refinement of the structure is currently in progress. We thank Prof. Venkatesan for the collaborative effort and for the benefit of his unpublished results.

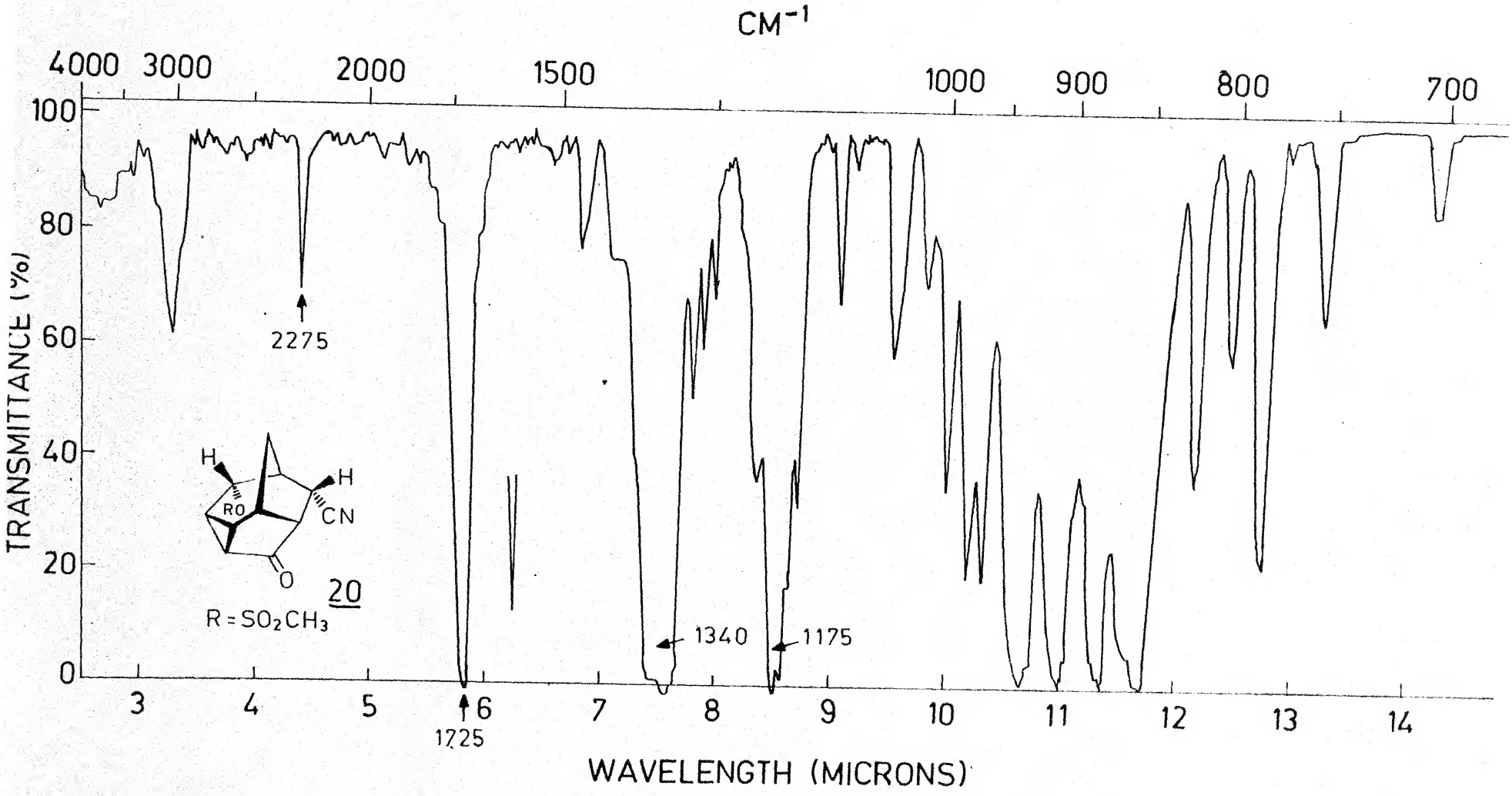


Fig. II.1. IR spectrum of 20

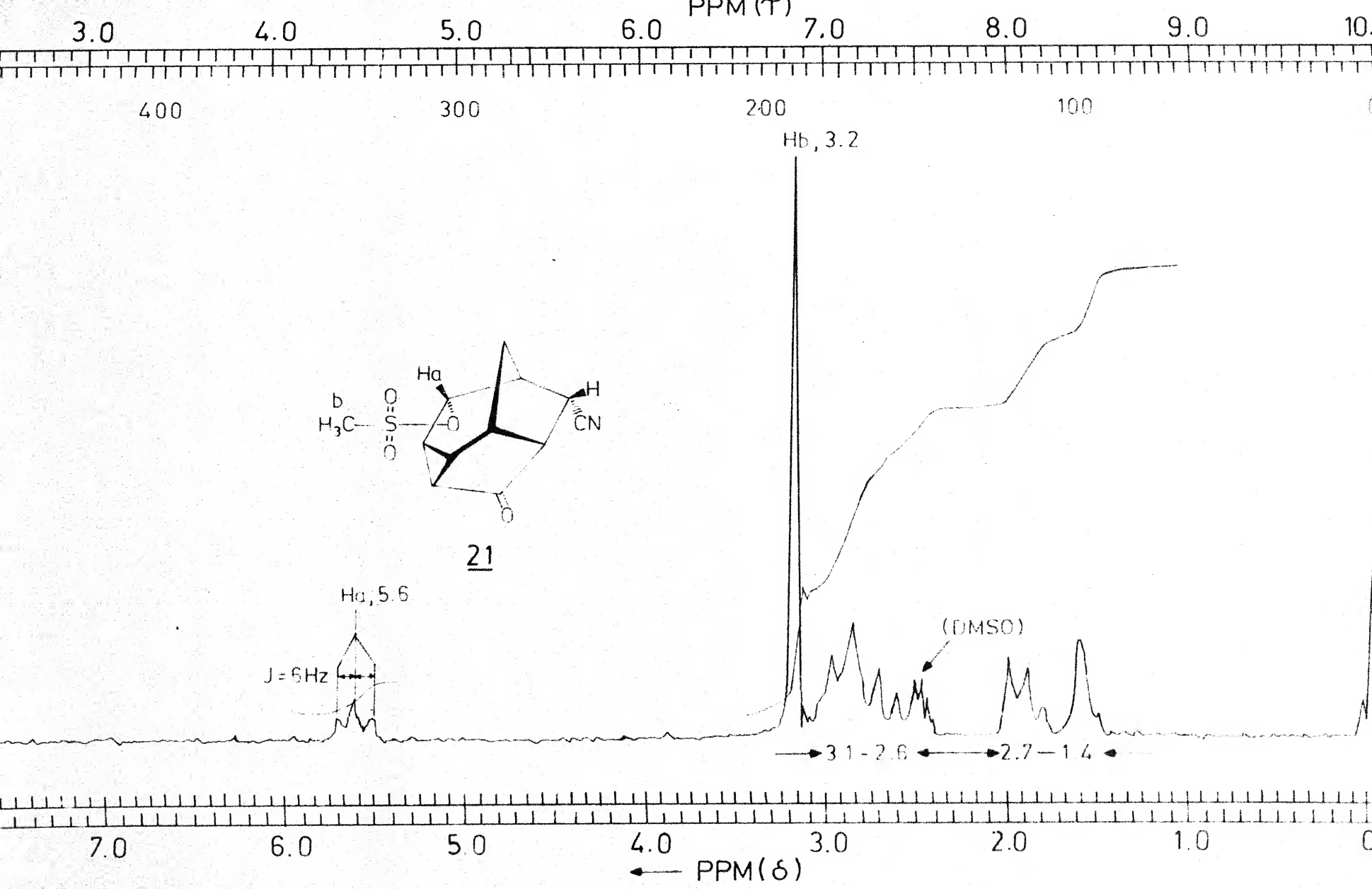


Fig. II.2 ^{1}H NMR spectrum (60MHz) of 21

J = 6 Hz) due to the methyl group and the proton adjacent to the methanesulphonoxy group. The appearance of the proton attached to the mesyloxy group at δ 5.6 showed considerable deviation[21] from its normally encountered position around δ ~ 5, indicating that it was attached to either an allylic or a cyclopropylcarbinyl carbon atom. The rest of the ^{1}H NMR spectrum consisted of a cluster of peaks between δ 1.4-3.1(9H) due to the rest of the ring protons. The ^{13}C NMR spectrum (Fig. II.3) displayed peaks at δ 210.1(s), 117.8(s), 78.9(d), 48.3(d), 40.3(d), 38.1(d), 34.6(t), 33.8(d), 33.5(d), 33.2(d), 28.5(d), 19.4(d).* The ^{13}C signals at δ 210.1, 117.8 and 78.9 could be readily assigned to the carbonyl carbon, cyanide carbon, and the carbon bearing the mesylate functionality respectively. There were no ^{13}C resonances due to olefinic sp^2 carbon atoms. The presence of a characteristic signal at δ 19.4 appeared diagnostic of a cyclopropyl carbon and supported the earlier surmise about the presence of a cyclopropylcarbinyl mesylate system. All the spectral data was thus indicative of a rearranged tetracyclic framework bearing a cyclopropane ring and structure 20 appeared to be the most logical formulation. However, in order to unravel the exact stereo-structure a direct single crystal X-ray analysis was carried out.

The crystals of the mesylate 20 used for X-ray diffraction were monoclinic and belonged to the space group $p2_1/a$ with

*Off-resonance multiplicities are indicated in parentheses.

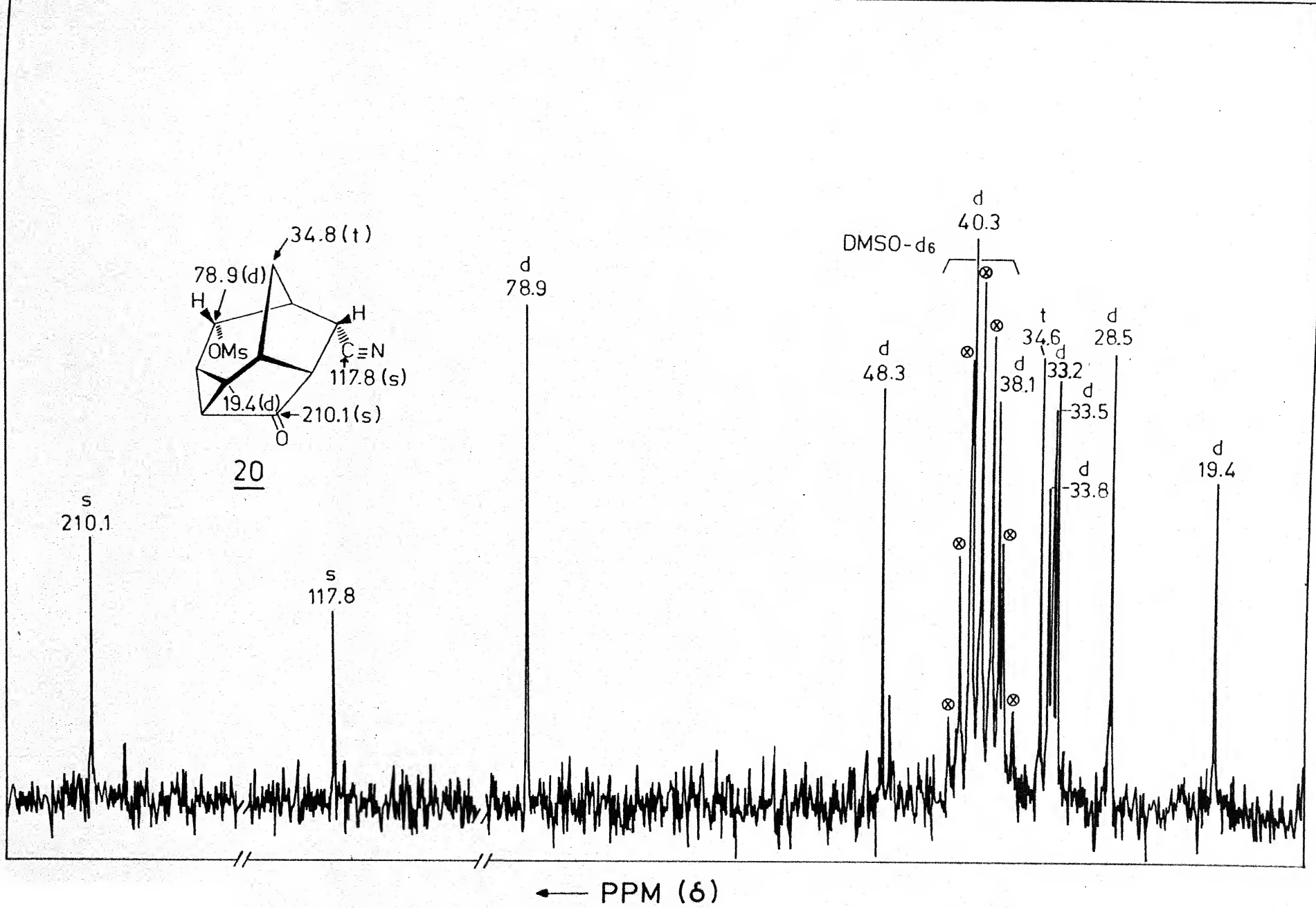


Fig. II.3. ^{13}C NMR spectrum (22.64MHz) of 20

a = 10.013, b = 9.620, c = 12.532 Å, β = 95.87° and the calculated density indicated four molecules per unit cell (Z = 4). Employing a crystal of 0.58 x 0.25 x 0.25 mm, a total of 1529 reflections having net amplitudes above their standard deviations were determined with MoK_α radiation using the moving crystal, moving counter technique on a CAD-4 diffractometer. The structure was solved by direct methods with the aid of programme MULTAN.[22] Seventeen out of the eighteen non-hydrogen atoms were located on an E-map calculated with phase-set having the lowest R_{Karle} value. The missing atom was located from a difference fourier map. Block-diagonal least-squares refinement of the positional and isotropic temperature factors of the non-hydrogen atoms converged at R = 13.5%. At this stage positions of all the hydrogen atoms were obtained from a difference fourier map. Further refinement of the positional and anisotropic temperature factors of the non-hydrogen atoms and the positional and isotropic temperature factors of the hydrogen atoms has brought down the R index to 0.038. A perspective view of the molecule is shown in Fig. II.4. Various bond lengths and bond angles are summarized in Tables II.1 and II.2.

The less polar mesylate, mp 171°C, obtained during Schmidt reaction of 1, was assigned structure 21 on the basis of the following spectral evidence. The molecular ion peak at m/e 267 confirmed the elemental composition $C_{12}H_{13}NO_4S$. The presence of diagnostic bands in the IR spectrum (Fig.II.5) at 2275 and at 1340 and 1175 cm^{-1} revealed the presence of the

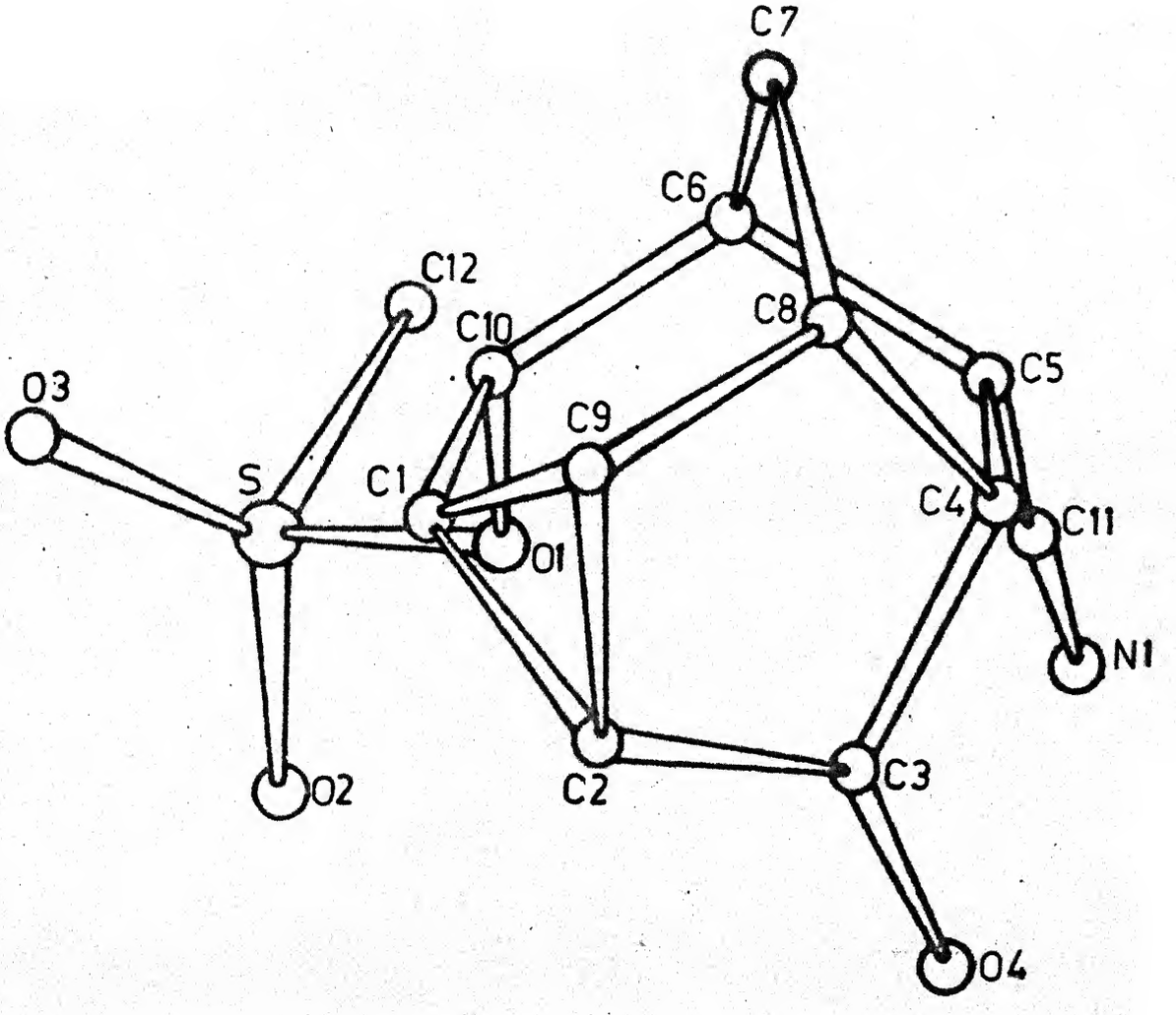


Fig. II.4 X-Ray crystal structure of 20

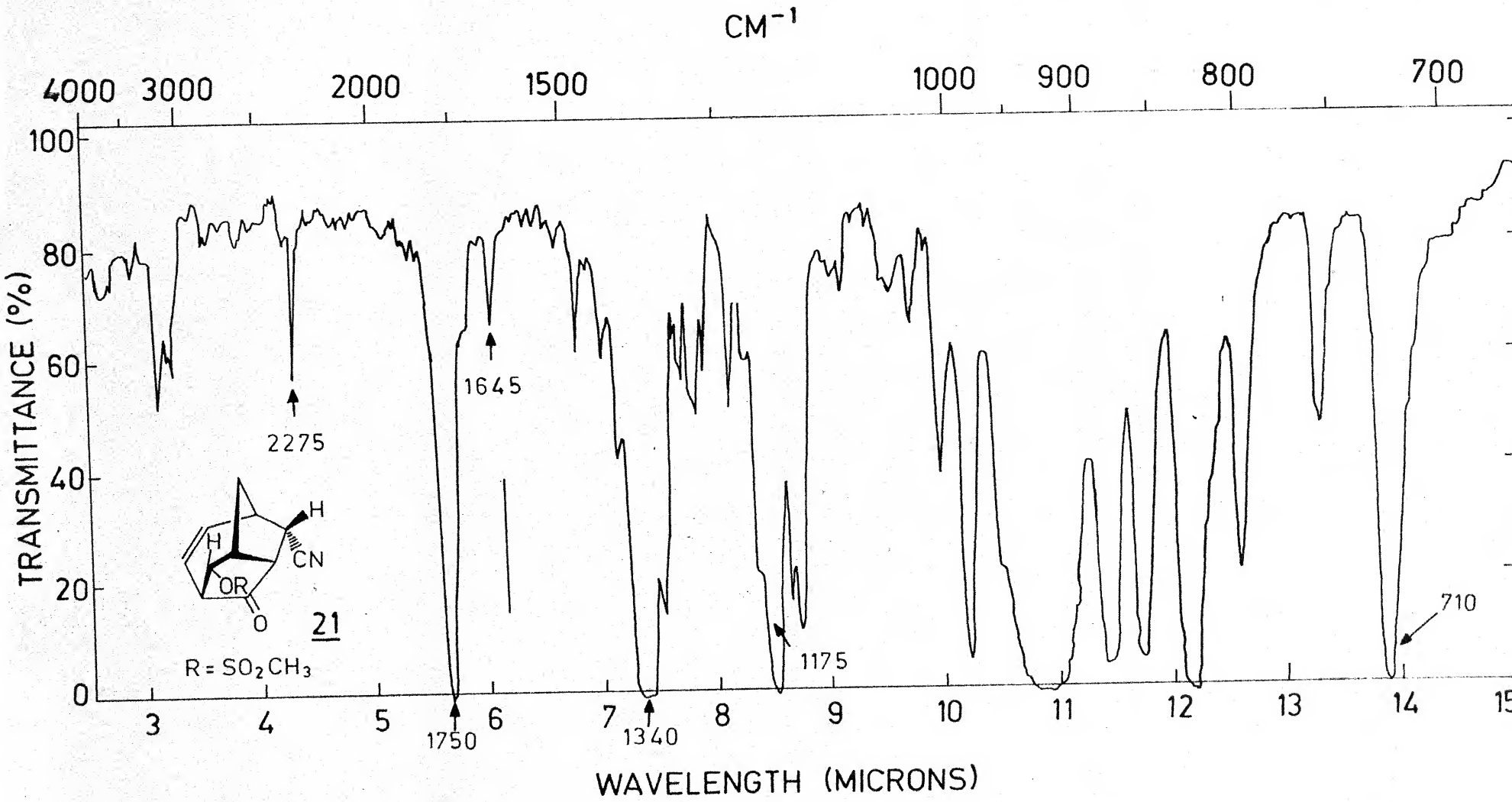


Fig. II.5. IR spectrum of 21

Table II.1

Bond Lengths (Å)

$S - C_{12}$	= 1.745	$C_4 - C_5$	= 1.544
$S - O_1$	= 1.566	$C_4 - C_8$	= 1.550
$S - O_2$	= 1.419	$C_5 - C_6$	= 1.542
$S - O_3$	= 1.403	$C_5 - C_{11}$	= 1.464
$C_1 - C_2$	= 1.533	$C_6 - C_7$	= 1.531
$C_1 - C_9$	= 1.486	$C_6 - C_{10}$	= 1.521
$C_1 - C_{10}$	= 1.491	$C_7 - C_8$	= 1.522
$C_2 - C_3$	= 1.460	$C_8 - C_9$	= 1.524
$C_2 - C_9$	= 1.508	$C_{10} - O_1$	= 1.485
$C_3 - O_4$	= 1.207	$C_{11} - N_1$	= 1.138
$C_3 - C_4$	= 1.513		

Accuracy $\approx$ 0.006 Å

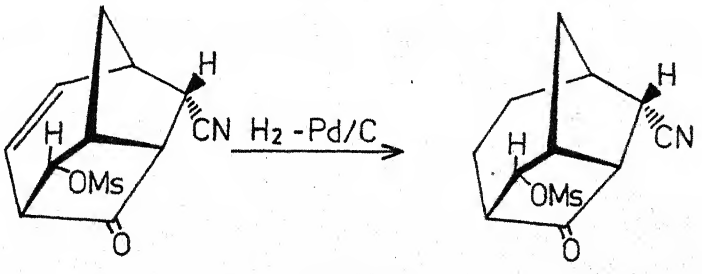
Table II.2

Bond Angles (^{o})

$C_{12}-S-O_1$	= 103.83	$C_4-C_5-C_6$	= 102.99
$C_{12}-S-O_3$	= 110.56	$C_4-C_5-C_{11}$	= 116.15
$C_{12}-S-O_2$	= 107.12	$C_6-C_5-C_{11}$	= 117.80
O_1-S-O_2	= 109.64	$C_5-C_6-C_{10}$	= 116.13
O_1-S-O_3	= 104.95	$C_5-C_6-C_7$	= 99.40
O_2-S-O_3	= 119.64	$C_7-C_6-C_{10}$	= 107.02
$C_2-C_1-C_9$	= 59.91	$C_6-C_7-C_8$	= 100.57
$C_2-C_1-C_{10}$	= 125.18	$C_4-C_8-C_9$	= 104.94
$C_9-C_1-C_{10}$	= 119.80	$C_4-C_8-C_7$	= 106.34
$C_1-C_2-C_9$	= 58.51	$C_7-C_8-C_9$	= 109.30
$C_1-C_2-C_3$	= 117.50	$C_1-C_9-C_8$	= 112.25
$C_3-C_2-C_9$	= 107.59	$C_2-C_9-C_8$	= 109.42
$C_2-C_3-C_4$	= 109.44	$C_1-C_9-C_2$	= 61.58
$C_4-C_3-O_4$	= 125.38	$C_6-C_{10}-C_1$	= 117.83
$C_2-C_3-O_4$	= 125.12	$C_6-C_{10}-O_1$	= 109.69
$C_5-C_4-C_8$	= 103.47	$C_1-C_{10}-O_1$	= 107.92
$C_3-C_4-C_8$	= 106.97	$C_5-C_{11}-N_1$	= 176.53
$C_3-C_4-C_5$	= 112.08	$S-O_1-C_{10}$	= 120.51

Accuracy $\approx$ 0.3-0.4^{o}

cyano and the mesylate group. Strong IR absorptions at 1750 and 710 cm^{-1} could be readily attributed to a five-membered cyclic ketone and a cis-disubstituted olefinic linkage. The presence of an olefinic double bond was further established by catalytic hydrogenation on 10% Pd-C which resulted in the uptake of 1 mole of hydrogen and the dihydro compound 22, mp 173° was obtained. The dihydro compound 22 was devoid of any olefinic protons in the proton NMR spectrum (Fig. II.6)



21 22

and being $C_{12}H_{15}NO_4S$ must be a tricyclic compound.

The ^1H NMR spectrum (270 MHz, DMSO-d_6) of 21 (Fig. II.7) was very well resolved and quite informative. It exhibited the presence of two olefinic protons at δ 6.31 (1H, t, $J_1 = J_2 =$ 10.5 Hz) and 5.94 (1H, t, $J_1 = J_2 =$ 10.5 Hz), a proton attached to the carbon bearing the methanesulphonoxy group at δ 4.94 (1H, s), methyl group of the mesylate ester at δ 3.26 (3H, s) and the methine proton attached to the cyano group at δ 3.52 (q, $J_1 =$ 11 Hz, $J_2 =$ 8 Hz) as the diagnostic resonances. In conformity with these assignments, the ^{13}C NMR spectrum (Fig. II.8) displayed signals at δ 211.1 (carbonyl), 138.1 and

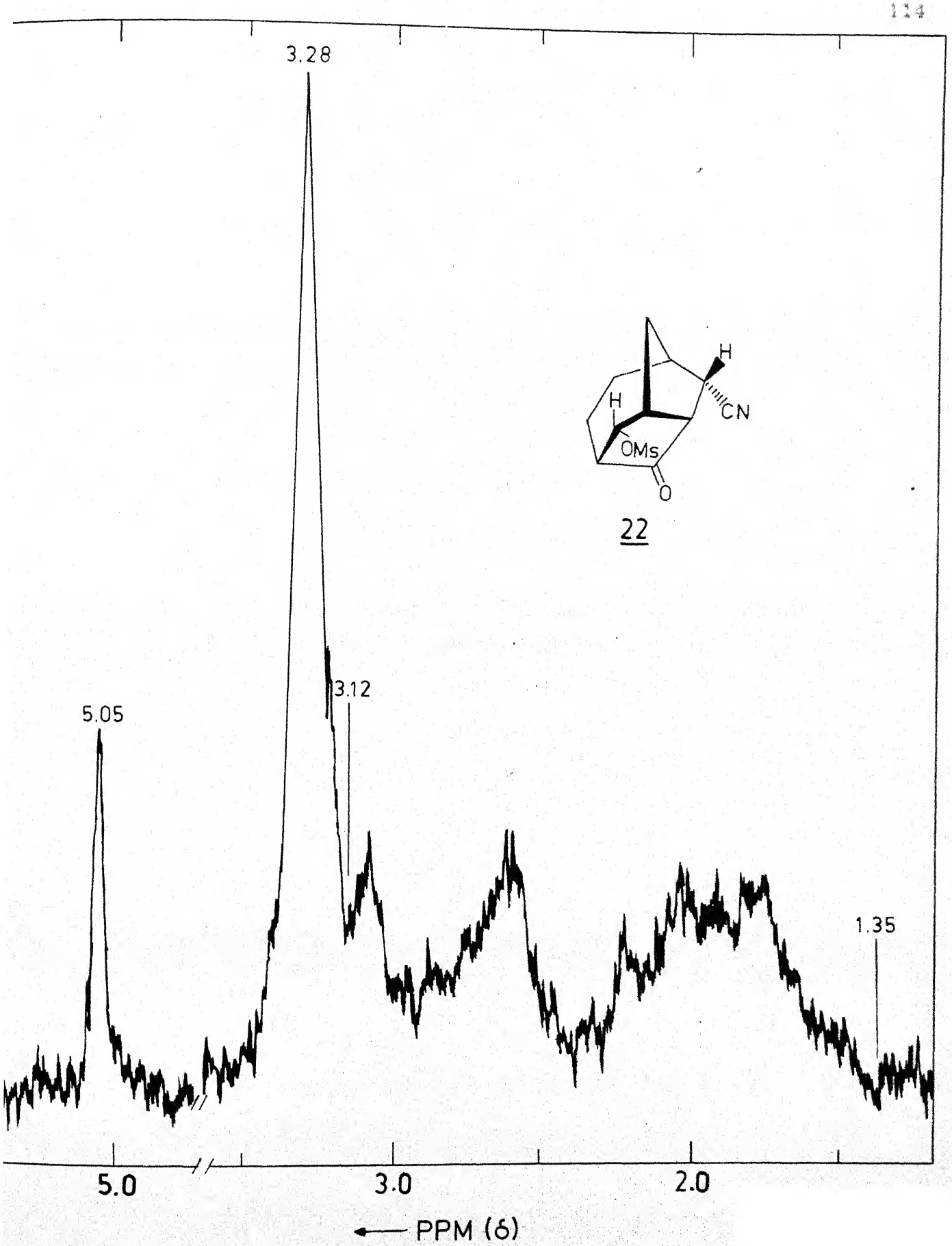


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Fig. II.6. ^{1}H NMR spectrum (60MHz) of 22

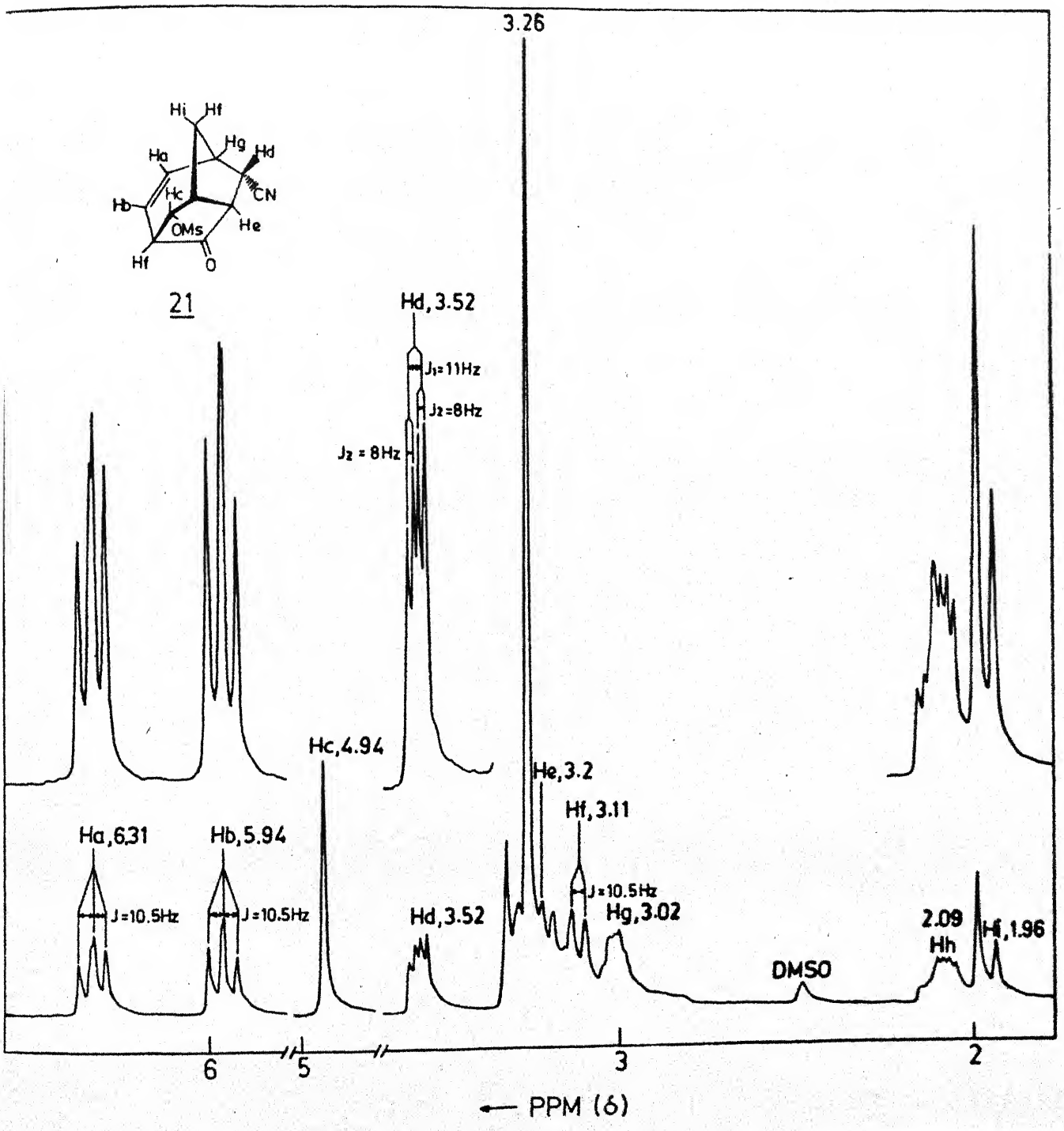


Fig. II.7 ^{1}H NMR spectrum (270Hz) of 21

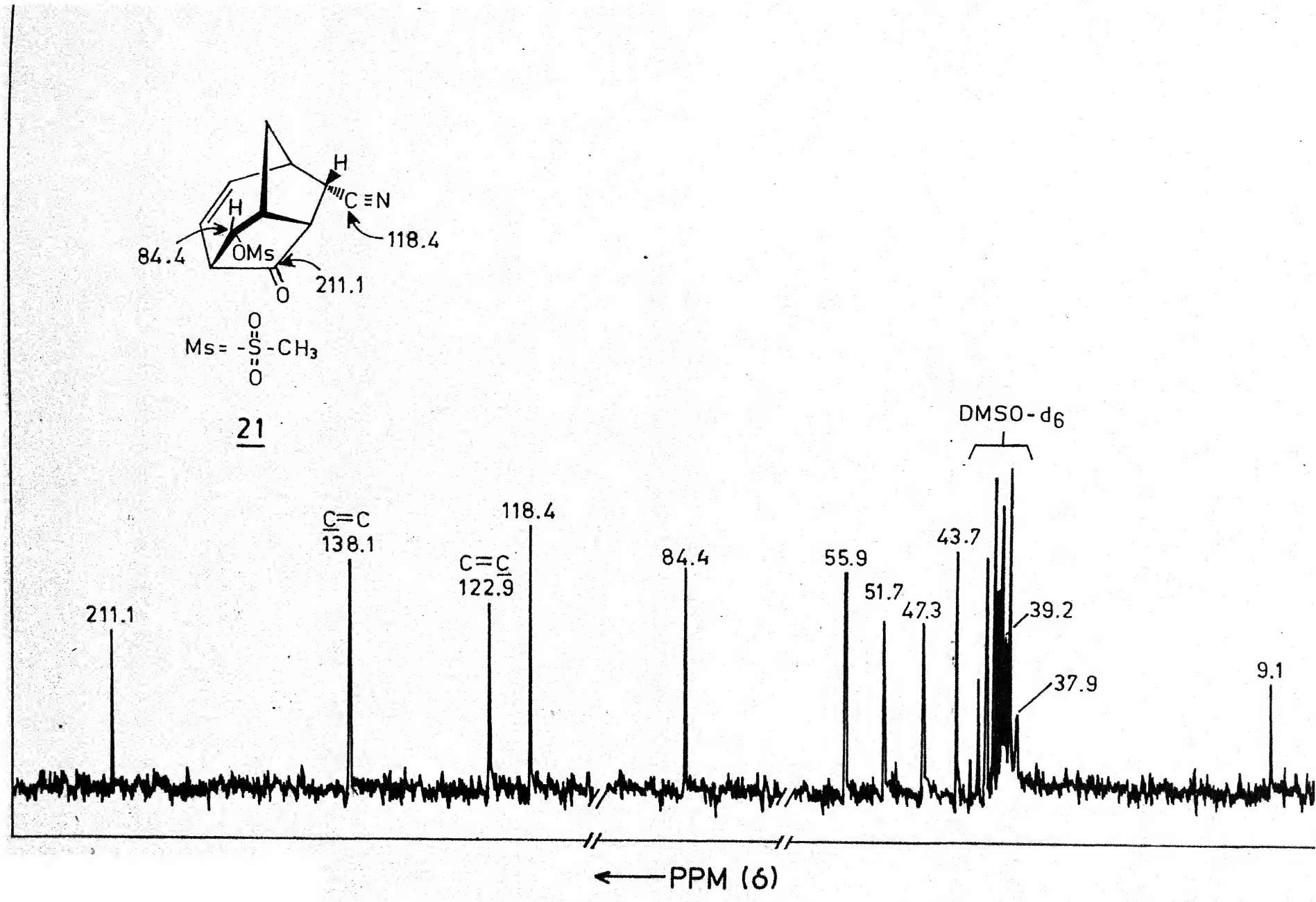
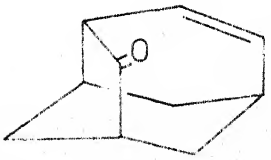


Fig. II.8 ^{13}C NMR spectrum (22.64MHz) of 21

122.9 (olefinic C-s), 118.4 (C≡N), 84.4 (C-O-S(=O)(=O)-CH_3) and 55.9, 51.7, 47.3, 43.7, 39.2, 37.9, 9.1 due to the rest of the seven carbons.

The above spectral data and in particular the remarkable resemblance of the ^{1}H NMR olefinic proton resonances in 21 with those of 2-proto-adamantenone (23)[23] and tricyclo[4.4.1.$0^{3,8}$]-undec-9-en-3-one (24)[24] suggested either the 3,7-ethanotricyclo-[3.3.0.$0^{3,7}$]octane (21) or the 2-protoadamantenone (25) formulation for this Schmidt fragmentation product. An unambiguous



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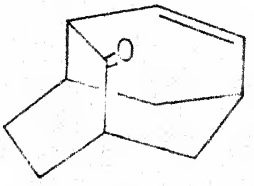

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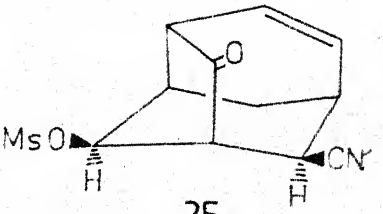


25

choice between 21 and 25 could be made on the following grounds.

It was possible to assign all proton resonances in the 270 MHz ^{1}H NMR spectrum of 21 with the aid of spin decoupling experiments. The results of spin decoupling experiments are summarized in Figs. II.7, II.9, II.10, and II.11, and the proton assignments are displayed on the structure 21 as displayed in Fig. II.7. The magnitude of various coupling constants and in particular of the olefinic protons $J_{cis\text{-}olefinic} = J_{vicinal} =$ 10.5 Hz observed here is in better agreement with 21 than 25 as gauged from various dihedral angles. In the case of

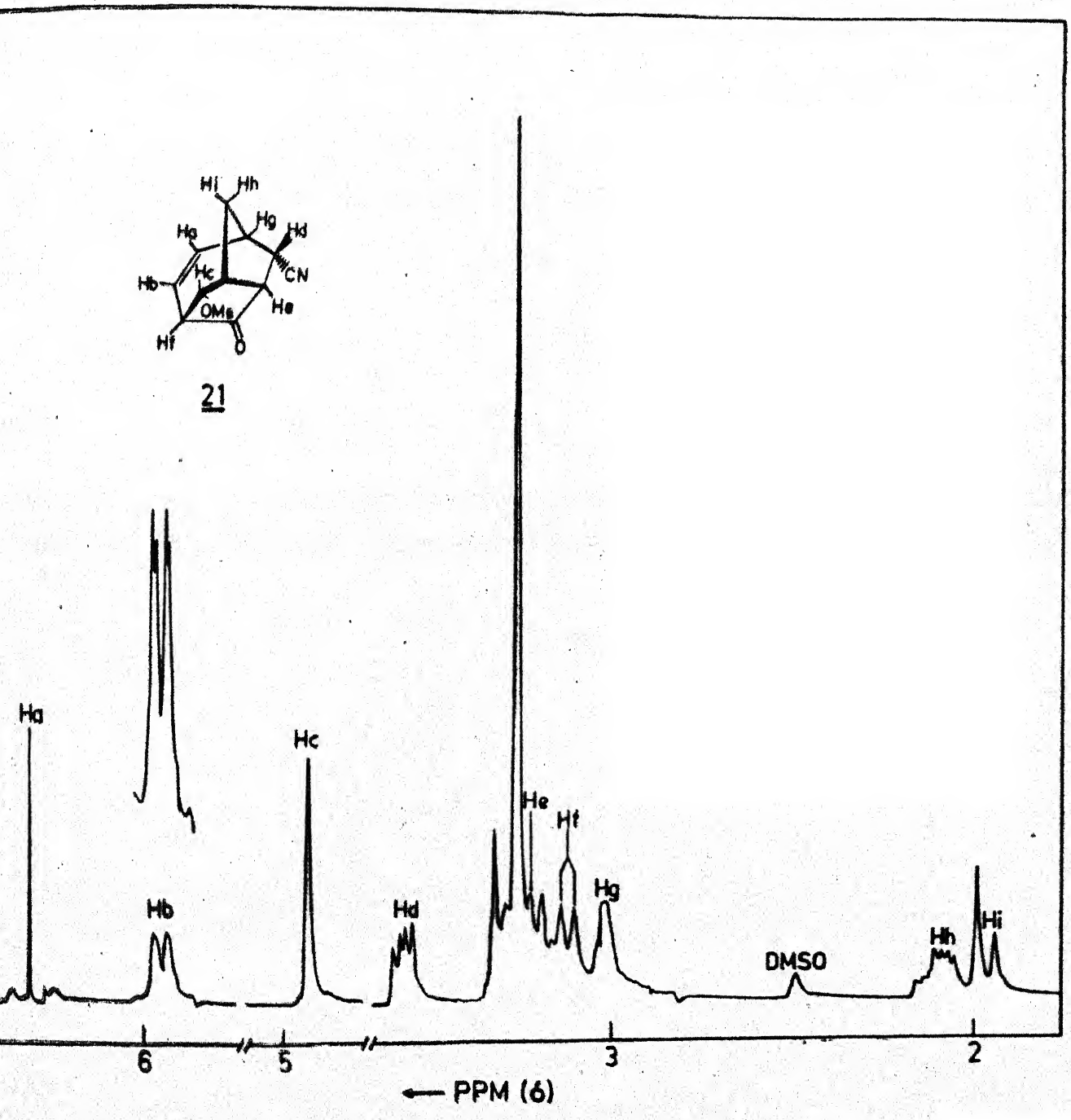
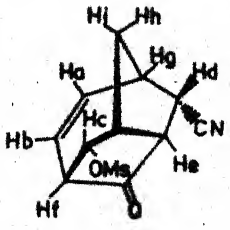


Fig.II.9 ^{1}H NMR spectrum (270MHz) of 21 decoupled from Ha.



21

Fig. II.10. ^{1}H NMR spectrum (270MHz) of 21 decoupled from Hb

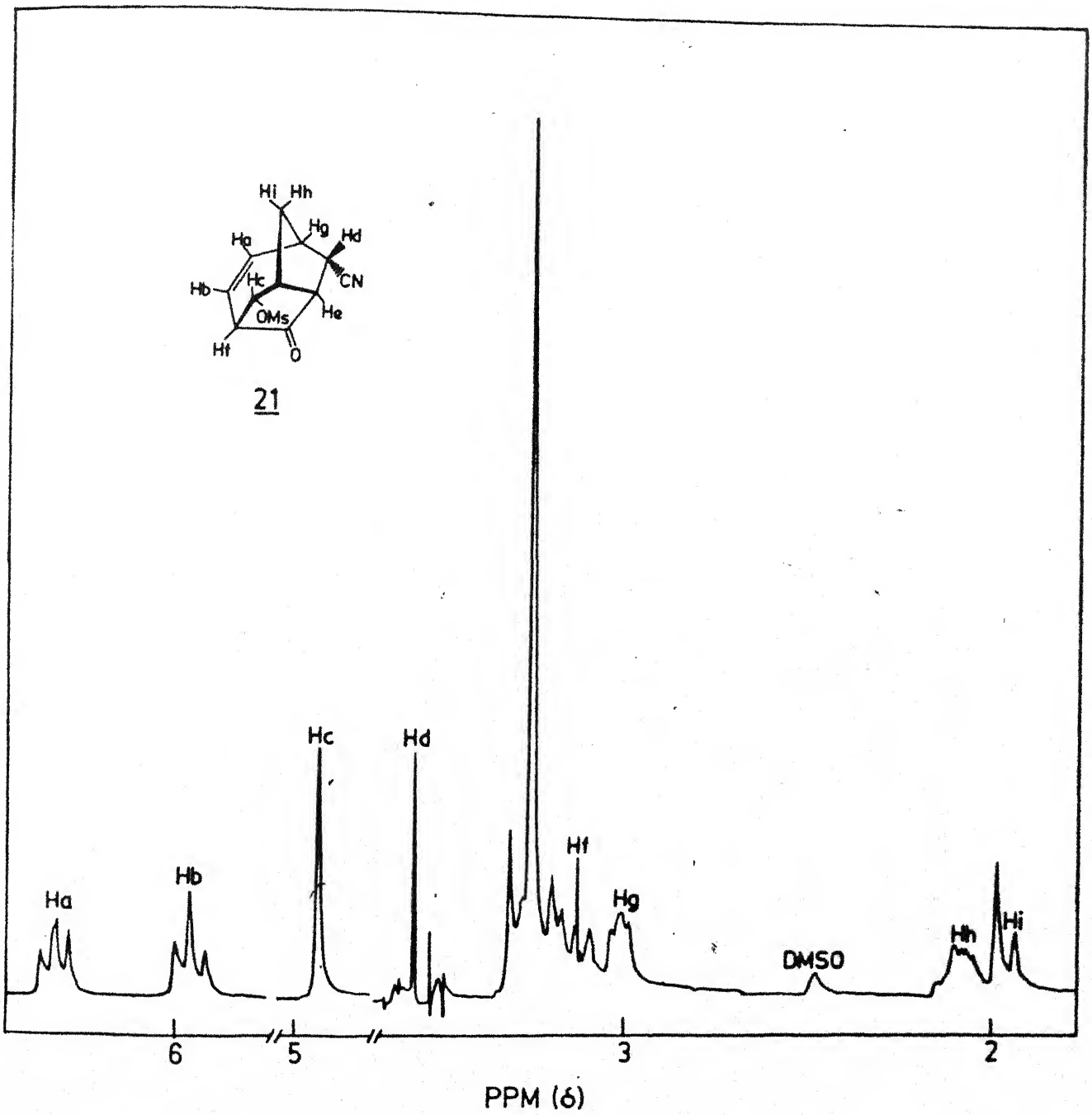
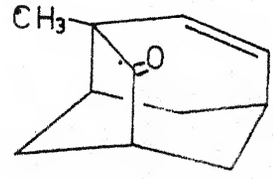


Fig. II.11. ^{1}H NMR spectrum (270MHz) of 21 decoupled from Hd

2-protoadamantenone derivatives 23, 26 and 27 the J_{vic} and $J_{cis\text{-}olefinic}$ coupling constants have been reported[23,25] in the range of 6-8 Hz. Similarly, the magnitude of other vicinal couplings was in better agreement with 21 than 25.



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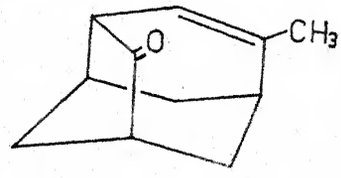

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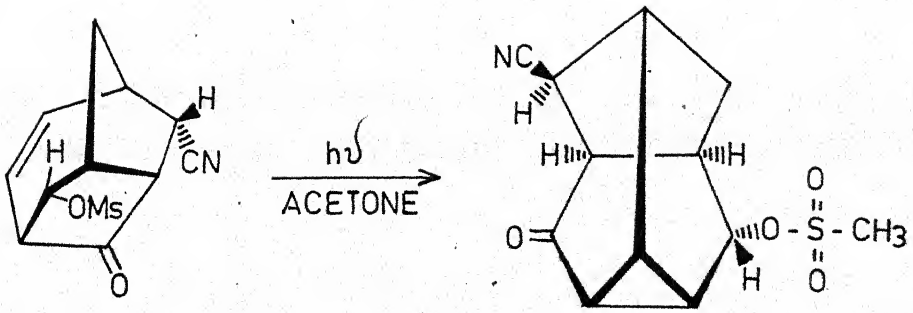
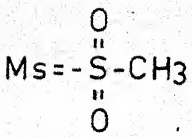
Further support for structure 21 was derived from the fact that it was quantitatively formed from 20 on solvolysis in methanesulphonic acid, the transformation representing a facile cyclopropylcarbinyl → homoallylic carbonium ion rearrangement.

Finally, sensitized photolysis of 21, which is a β , γ - unsaturated ketone, led to a smooth oxa-di-π- methane rearrangement[26] to the tetracyclic compound 28, mp 194° (Scheme II.8). As expected, 28 was devoid of any olefinic proton resonance in the ^{1}H NMR spectrum. In fact, the proton spectrum of 28 (Fig. II.12) consisted of only three sets of signals, a one proton multiplet at δ 5.25 (H-C-OMs), a three proton singlet at δ 3.18 (CH_3-$\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}$-O) and a complex envelope between δ 1.5-3.42 (CH, s). The ^{13}C NMR spectrum (Fig. II.13) exhibited resonances at δ 205.23 (s, C=O), 119.71 (s, C≡N), 80.39 (d, H-C-OMs), 37.9 (q, CH_3-$\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}$-O) and 49.19, 42.04, 40.38, 36.39, 35.09, 30.08, 29.44 (rest of the 8 C-s). This facile and interesting photochemical

Scheme II.8



21 28



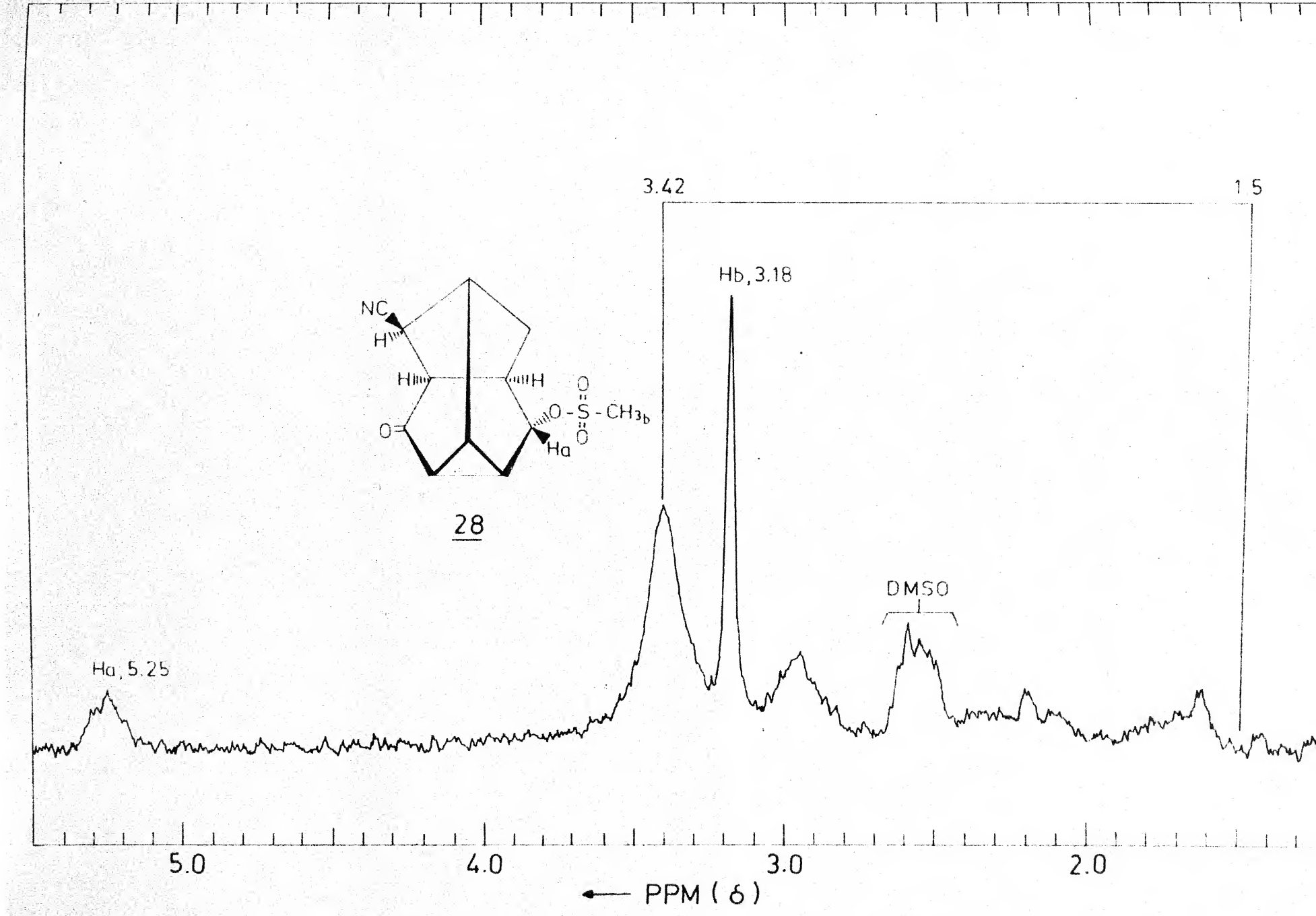


Fig. II.12. ^{1}H NMR spectrum (60MHz) of 28

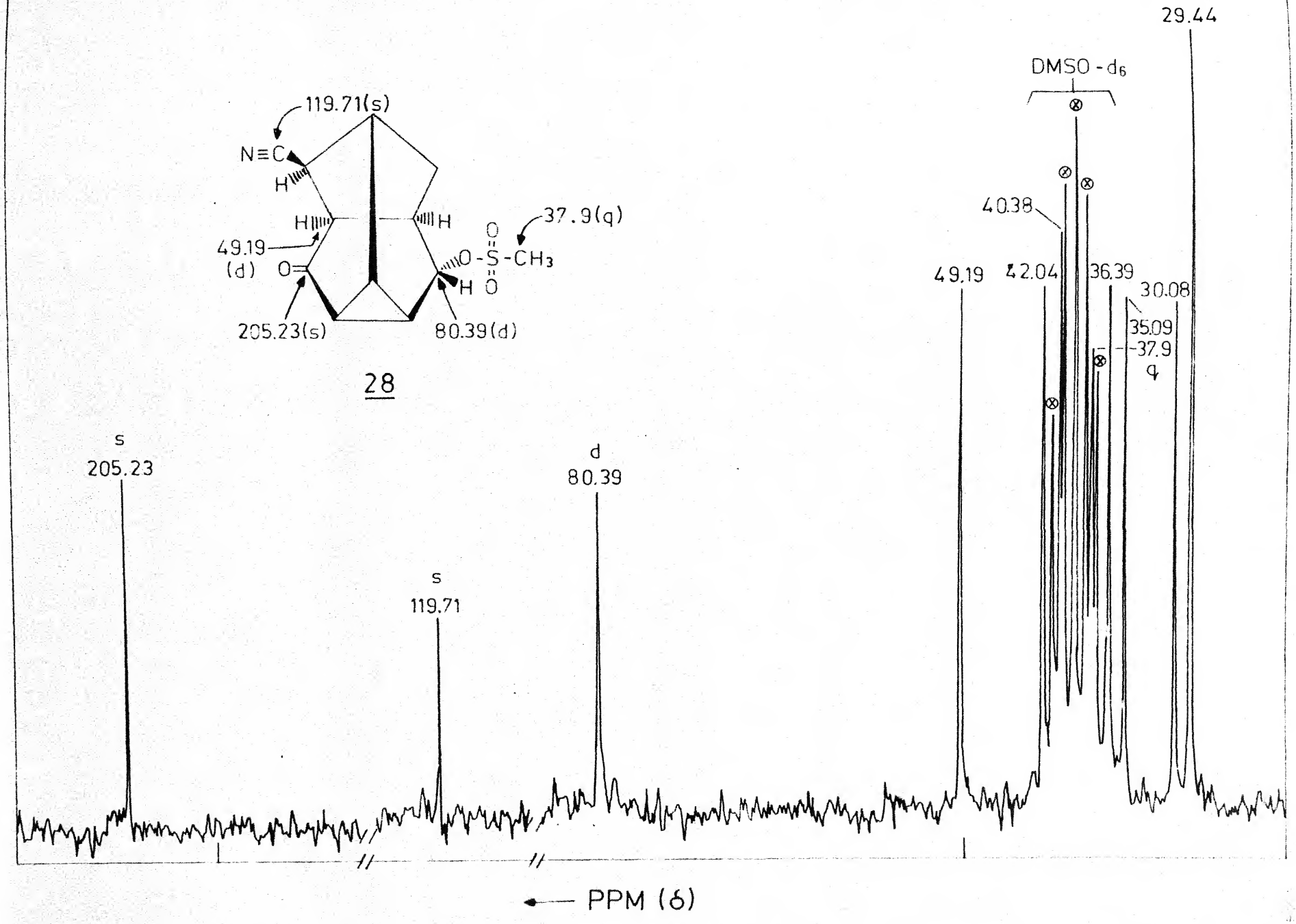


Fig. II.13. ^{13}C NMR spectrum (22.63MHz) of 28

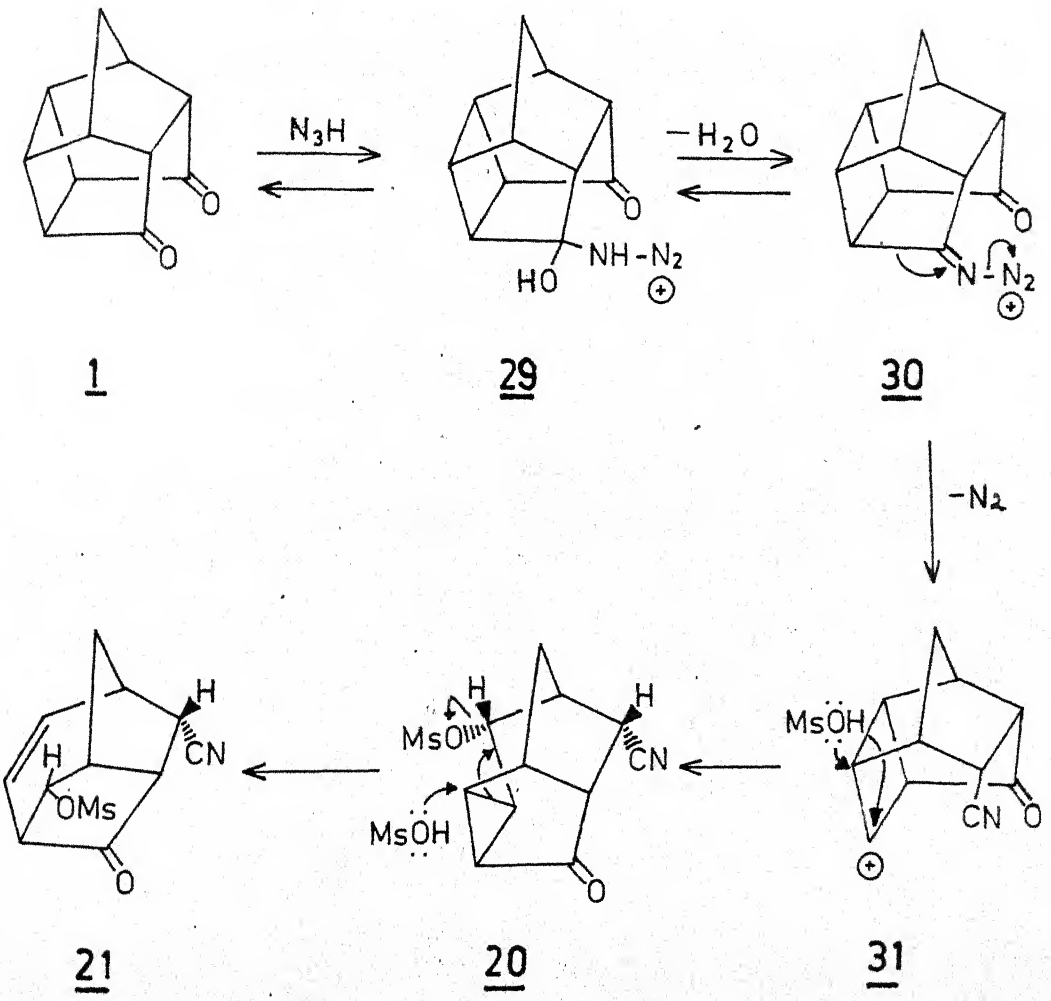
rearrangement of 21 further confirms its structure and provides facile entry to this interesting tetracyclic system.

A reasonable mechanism for the formation of mesylates 20 and 21 from the pentacyclic dione 1 during Schmidt reaction conditions (CH_3-SO_2OH-NaN_3) is depicted in Scheme II.9. The key intermediate 29 for Schmidt fission is readily formed via nucleophilic addition of azide ion (N_3^-) to the protonated carbonyl of 1, to azidohydrin 30 followed by acid-catalysed dehydration. Loss of nitrogen and fragmentation of 29 leads to the cyclobutyl carbonium ion 31 which quickly rearranges to the cyclopropylcarbinyl carbonium ion with concomitant nucleophilic capture to furnish the endo-mesylate 20. The observed stereochemistry of 20 is in agreement with this process. The mesylate 20 undergoes, in the medium, a methanesulphonic acid mediated stereospecific cyclopropylcarbinyl $\longrightarrow$ homoallylic carbonium ion rearrangement. The observed stereochemistry of the mesylate group in 21 favours a concerted mechanism. It is interesting to note here that the ring system present in 21 has been mentioned in the tricyclodecane graph as a possible precursor of adamantane.[27,28]

II.4 Experimental Section

The 270 MHz ^1H NMR and ^{13}C NMR spectra (22.64 MHz) were recorded on a Bruker WH-90 spectrometer. The infrared spectra were recorded on a Perkin-Elmer Model-137B spectrophotometer as KBr discs.

Scheme II.9



Schmidt Reaction of Diketone (1)

A solution of the diketone (1, 2.5 g, 14.37 mmol) in dichloromethane (25 ml) and methanesulphonic acid (8 ml) was cooled to 0-5°C. To it was added sodium azide (1.33 g, 20.46 mmol) in small quantities. The mixture was stirred for 2 hrs. when reaction was complete. It was poured into ice-cold water, and extracted with dichloromethane (25 ml x 3). The organic layer was washed with sodium bicarbonate solution and finally with brine and dried over anhydrous sodium sulphate. Removal of solvent gave a dark brown syrupy liquid (2 g). This was taken up in benzene-ethyl acetate mixture and chromatographed on silica gel (70 g). Elution with 95% benzene and 5% ethyl acetate mixture gave 20 (0.3 g, 15%), m.p. 179°C.

Mass spectrum: m/e 267, Molecular Formula: $C_{12}H_{13}NO_4S$.

UV spectrum, λ_{max}^{EtOH}: 275-280 nm($\varepsilon \simeq 35$, A = 0.85), 210 nm ($\varepsilon = 3240$, A = 1.592).

IR spectrum (KBr), ν_{max}: 2275 (cyano), 1725 (carbonyl), 1340, 1175 cm^{-1} (methanesulphonxy).

^1H NMR spectrum (60 MHz, DMSO-d_6): δ 1.4-3.1 (ring CH, 9H, en), 3.20 ($CH_3-\overset{O}{\overset{\|}{S}}(=O)-O$, 3H, s), 5.6 (H-C-OMs, 1H, t, J = 6 Hz).

^{13}C NMR spectrum (DMSO-d_6): δ 210.1(s), 117.8(s), 78.9(d), 48.3(d), 40.3(d), 38.1(d), 34.6(t), 33.8(d), 33.5(d), 33.2(d), 28.5(d), 19.4(d)

Further elution with the same solvent followed by elution with 90% benzene and 10% ethyl acetate mixture gave 21 (0.25 g, 10%), m.p. 171°C.

IR spectrum (KBr), ν_{max}: 2275 (cyano), 1750 (carbonyl), 1340, 1175 (methanesulphonoxy), 710 cm^{-1} (cis-disubstituted olefin).

^1H NMR spectrum (270 MHz, DMSO-d_6): δ 1.96(H-C-H, 1H, d, J = 13 Hz), 2.09 (H-C-H, 1H, m), 3.02 (ring CH, 1H, m), 3.11 (1H, d, J = 10.5 Hz), 3.2 (ring CH, 1H), 3.26 ($CH_3-\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}-O$, 3H, s), 3.35(ring CH, 1H, s), 3.52 (H-C-CN, 1H, q, J = 11 Hz), J_2 = 8 Hz, 4.94 (H-C-OMs, 1H, s), 5.94 (1H, t, J = 10.5 Hz), 6.31 (1H, t, J = 10.5 Hz).

^{13}C NMR spectrum (DMSO-d_6): δ 211.1 (C=O), 138.1 and 122.9 (C=C), 118.4 (C≡N), 84.4, 55.9, 51.7, 47.3, 43.7, 39.2, 37.9, 9.1.

Photolysis of 21

A solution of 21 (0.15 g, 0.56 mmol) in acetone (150 ml) was purged with a slow stream of purified nitrogen for 20 minutes. The solution was then irradiated with a 450 W Hanovia medium pressure mercury arc lamp for 8 hrs. in a pyrex immersion well. Removal of solvent and direct crystallization from acetone gave white crystals of 28 (0.12 g, 80%) m.p. 195°.

IR spectrum (KBr); ν_{max}: 2270 (cyano), 1750 cm^{-1} (carbonyl).

^{1}H NMR spectrum (60 MHz, DMSO-d_6): δ 1.5-3.42(ring CH, complex en), 3.18 ($\underline{CH_3}$-$\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}$-O, 3H, s), 5.25 (H-C-OMs, 1H, m).

^{13}C NMR spectrum (DMSO-d_6): δ 205.23 (s, C=O), 119.71 (s, -C≡N), 80.39 (d, H-C-OMs), 37.9 (q, $\underline{CH_3}$-$\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}$-O), and 49.19, 42.04, 40.38, 36.39, 35.09, 30.08, 29.44 (unassigned 8 C's).

Hydrogenation of 21

A solution of 21 (0.135 g, 0.50 mmol) in ethyl acetate (20 ml) was hydrogenated in the presence of 10% Pd/C as catalyst. 13 ml of hydrogen was consumed. Filtration of the catalyst and evaporation of solvent gave (22). On crystallization from methylene chloride-ether mixture yielded 22 (0.1 g, 74%), m.p. 173°C.

IR spectrum(KBr), ν_{max}: 2270 (cyano), 1750 (carbonyl), 1360, 1175 cm^{-1} (methanesulphonoxy).

^{1}H NMR spectrum (60 MHz, DMSO-d_6): δ 1.35-3.12 (8H, en), 3.28 (-O-$\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}$-$\underline{CH_3}$, 3H, s), 5.05 (H-C-OMs, 1H, s).

Transformation of 20 to 21

To a solution of 20 (0.1 g, 0.37 mmol) in methylene chloride (8 ml) was added methanesulphonic acid (2 ml). The solution was refluxed for 3 hrs. After cooling it was poured into aqueous sodium bicarbonate solution and extracted with methylene chloride (10 cc x 3). After washing with brine and

drying over anhydrous sodium sulphate, evaporation of solvent gave 21 (95 mg, 95%), m.p. 171°C.

IR spectrum (KBr), ν_{max}: 2275 (cyano), 1750 (carbonyl), 1340, 1175 (methanesulphoxy), 710 cm^{-1} (cis-disubstituted olefin).

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CHAPTER III

REVELATION OF PENTACYCLO[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]UNDECANE ⇌ OXA-BIRD CAGE EQUILIBRIUM BY ^{13}C NMR SPECTROSCOPY AND LEAD TETRAACETATE FRAGMENTATION OF SOME POLYCYCLIC SYSTEMS

III.1 Abstract

^{13}C NMR spectra of several derivatives, particularly the hydrates, derived from pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]-undecane-8,11-dione (1) and pentacyclo[6.4.0.$0^{2,7}$.$0^{3,11}$.$0^{6,10}$]-dodecane-9,12-dione (2) have been studied. It has been established that the hydrate derived from 1 is an intimate mixture of monohydrated ketone (16) and the transannularly cyclized dihydroxy ether (3) bearing an oxa-bird cage skeleton. In a similar manner, the ketol (11) obtained via sodium borohydride reduction of 1 has been shown with the aid of ^{13}C NMR spectroscopy to be an equilibrium mixture of the pentacyclic structure (11) and the oxa-bird cage form (14). Previously assigned structure to the hydrate (4) from homologous dione (2) has been verified.

Lead tetraacetate oxidation of hydrates (3 + 16) and (4) has been investigated. The former furnishes a novel lactone (28) in high yield via a carbonium ion rearrangement and intramolecular lactonization. The hydrate (4) furnishes an unsaturated anhydride (29) bearing a tricyclo[4.2.2.$O^{2,5}$]decane framework and a lactone (30) related to dione (2). Structures to these products have been assigned on the basis of complementary spectroscopic evidence, and plausible mechanism is suggested for their formation.

III.2 Introduction

In the previous chapters of this thesis, it has been demonstrated that the pentacyclic dione (1), readily available[1] from the cyclopentadiene-p-benzoquinone Diels-Alder adduct, can serve as a useful precursor to a variety of interesting and novel carbocyclic systems. The rearrangements of 1 described earlier[2] were mediated through carbonium ion intermediate and involved cyclobutyl → cyclopropylcarbinyl → homoallylic carbonium ion type of rearrangements. We conceived another approach emanating from 1 which could provide an unconventional but purposeful alternate route to cubyl-caged systems* and their

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*Conventionally, cubyl-caged systems have been prepared through multi-step and painstaking elaboration of cyclopentadienone dimers,[3-6] cyclopentadiene-maleic anhydride adducts[7-9] and cyclobutadiene-p-benzoquinone cycloaddition products.[10,11] These approaches, though elegant in conception and brilliantly executed, are either expensive or lengthy and tedious for large-scale preparations. Therefore, the development of rather less expensive and more flexible routes to cubyl systems was contemplated. Recently, a novel and practical approach to basketane (1,1'-bishomocubane) utilizing 1,3-cyclohexadiene-p-benzoquinone adduct has been described.[12]

fused cyclobutene precursors. The sequence dipicted in Scheme III.1 attempts to exploit the transannular proximity of the two carbonyl groups in the caged, space-enclosing framework of 1 and its congeners.

The synthetic methodology for the acquisition of starting materials 1* and 2** is very well worked out and these can be rendered available, in quantity, quite expeditiously (Scheme III.2). There is ample precedence for the oxidative decarboxylation step (5 → 6) and can be effected quite efficiently through a variety of available methods,[13] e.g. lead tetraacetate bisdecarboxylation[14] and its various modifications,[15-17] electrolytic oxidative bisdecarboxylation,[18,19] di-ter-butyl perester decomposition,[20] thermal process using dicarbonyl bis(triphenylphosphine)nickel,[21-23] cuprous oxide-quinoline reagent.[24] etc. Thus, the success or failure of the Scheme III.1 depends mainly on the ease of transannular hydration (1 → 3 and 2 → 4) and the effectiveness of the fragmentation reaction (3 or 4 → 5). These two aspects, therefore, need to be discussed in the introductory section.

Taking the fragmentation reaction (3 or 4 → 5) first, such a reaction could be brought about by lead tetraacetate (LTA) or Ce^{+4} based reagents. Many examples of analogous fragmentation process mediated through LTA are reported in literature. Two

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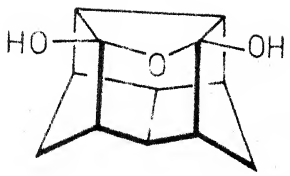
* Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione.

**Pentacyclo[6.4.0.0^{2,7}.0^{3,11}.0^{6,10}]dodecane-9,12-dione.

noteworthy examples[25,26] which have a bearing on the 3 or 4 → 5 step of our Scheme III.1 are depicted in Scheme III.3. Amongst these, the 9 → 10 transformation employed by Woodward, Fukunaga and Kelly as the key step in triquinacene synthesis could be considered as the seminal example. These examples reinforced our confidence in the success of the LTA fragmentation reaction, once the structures of the precursor polycyclic dihydroxy ethers 3 and 4 were firmly secured.

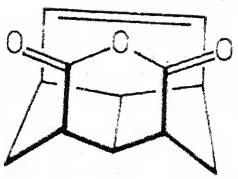
During his pioneering studies on intramolecular photocycloadditions, Cookson and his group[1] not only devised convenient and high-yield synthesis of 1 and 2 but also studied several physical and chemical characteristics of these interesting ring systems. For example, it was shown[1] on the basis of UV and IR spectral data that there is considerable "through space" electronic interaction between the two transannularly disposed carbonyl groups of 1 and 2. Cookson also demonstrated that on exposure to air (18 months!) both the diones 1 and 2 formed insoluble monohydrates, which showed no carbonyl absorption in the IR spectra and reverted to the original diones on heating. Based on this evidence, the two hydrates from 1 and 2 were formulated as 3 and 4, respectively. It was further observed[1] that 4 was formed more readily than 3 but lost water reluctantly on heating to 150°C as compared to 80°C for 3, thus "... reflecting favourable intercarbonyl distance and angle in 2 relative to 1." Cookson and his collaborators investigated the

Scheme III.3



9

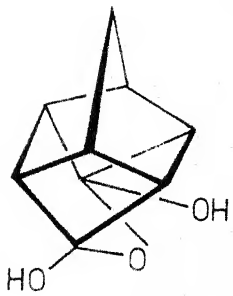
LTA
Benzne



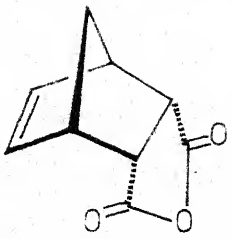
10

Reference

25

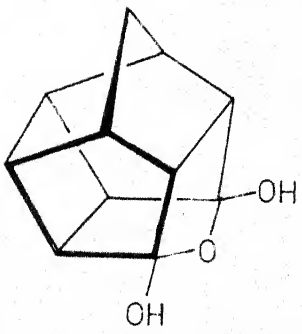


LTA
Benzne

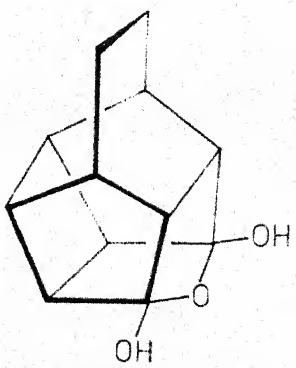


26

O



3



4

$NaBH_4$ reduction of pentacyclic dione 1 and found that it furnished a mixture of hydroxy-ketone (11, ketol) and the diols 12 and 13 (Scheme III.4). The ketol (11) was shown[1] to exist exclusively in the open form on the basis of its carbonyl absorption (1710 cm^{-1}) in the IR spectrum and no evidence could be adduced for any contribution from the transannularly formed cyclic hemi-acetal (14). The structure 3, assigned to the hydrate of the dione (1) by Cookson, as well as structure 14 bear a skeletal relationship to the "bird-cage" system 15 of Winstein[27,28] and can be termed as its heterocyclic analogue, the oxa-bird cage system.* In a study directed towards the preparation of the oxa-bird cage system and related hetero-cage compounds, the Japanese group[29,30] of Sasaki attempted to exploit the transannular reactivity of the two carbonyl groups in 1 as shown in Scheme III.5. This approach was obviously patterned after the earlier observation[1] of Cookson that dione (1) adds a molecule of water to furnish the transannular hydrate (3). However on subjecting 1 to hydration, Sasaki et al.[30] obtained a monohydrate whose spectral properties were in disagreement with the earlier formulation 3 of Cookson. For example, Sasaki's hydrate displayed strong IR absorptions due to hydroxyl and carbonyl groups at 3300 and 1715 cm^{-1}. On heating, this hydrate was reconverted to the starting dione (1) with loss of water and no trace of transannularly cyclized hydrate (3) could be detected.

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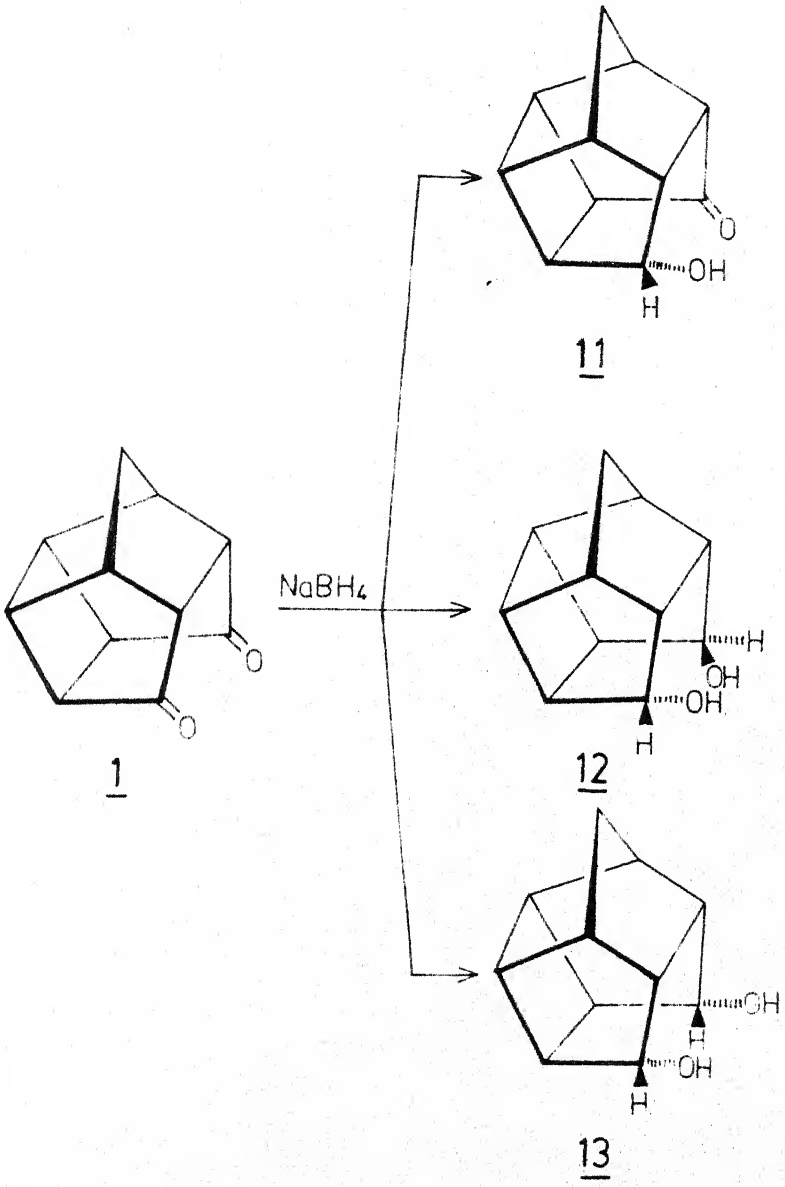
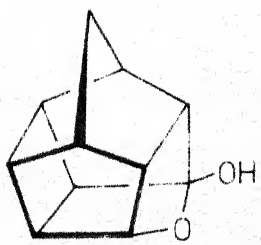
*4-Oxa-hexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane.

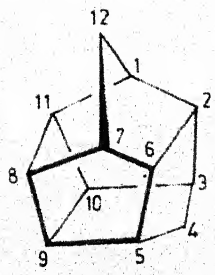
Scheme III.4



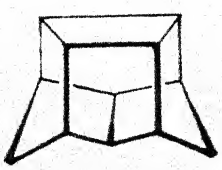
1 11 12 13



14

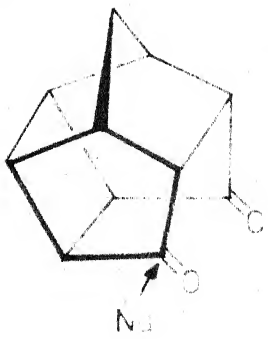


15 ≡

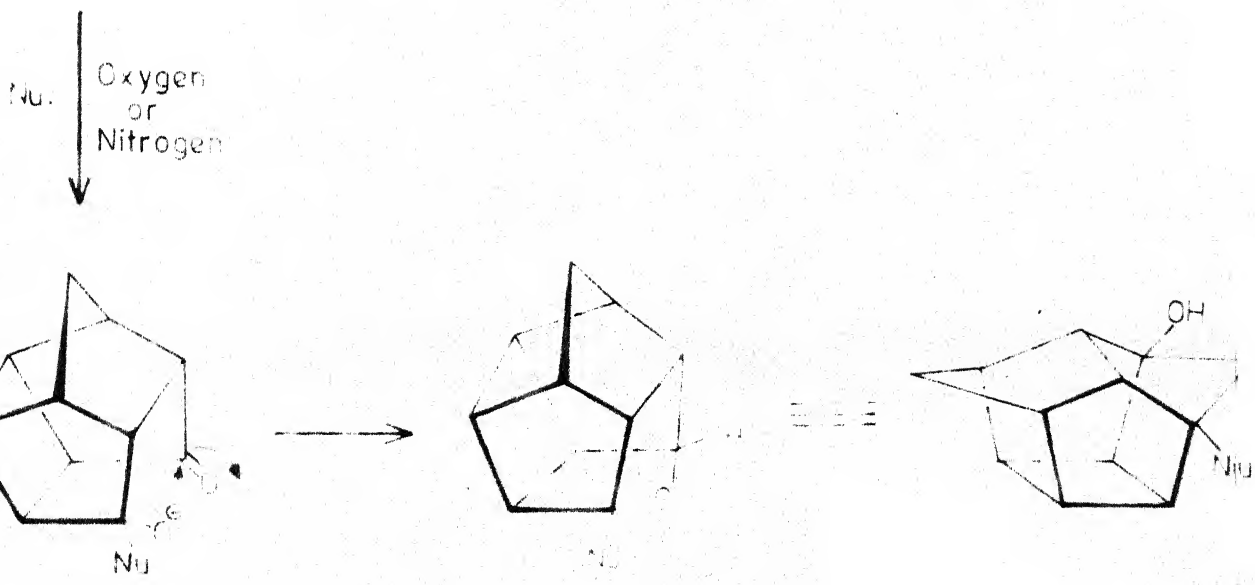


15

Scheme III.5

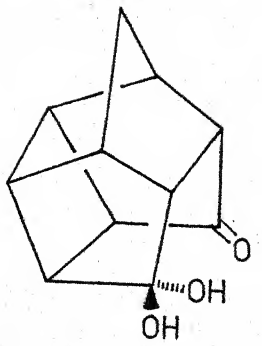


1



The Japanese group, thus, assigned structure 16 to the hydrate obtained by them from 1. Concurrently with the reformulation of the monohydrate from 1 as 16, Sasaki confirmed[30] the earlier report about the sodium borohydride reduction of dione (1) furnishing a mixture of diols (12) and (13) along with the ketol (11). The ketol was specifically shown to exist in the open form 11 and according to them[30] showed no tendency towards internal hemi-ketalization to the oxa-bird cage form 14. This led to the surmise that the pentacyclic system 1 has much lower transannular cyclization ability as compared to other polycyclic systems, e.g. the bicyclo(3.3.1)nonane system. In this system, for example, it is known[31,32] that sodium borohydride reduction of bicyclo(3.3.1)nonane-3,7-dione (17) furnished the hemi-ketal (18) *via* transannular nucleophilic addition. Several other examples of transannular hemi-ketal formation in polycyclic systems have been cited in literature and some of them are shown in Scheme III.6. However, lack of such transannular reactivity in 1 was attributed[30] to unfavourable bond angles and distances. During the above mentioned studies on the transannular reactivity of system 1, the homologous system 2 was not investigated and the only evidence available[1] about its transannular hydration to 4 was that originally described by Cookson.

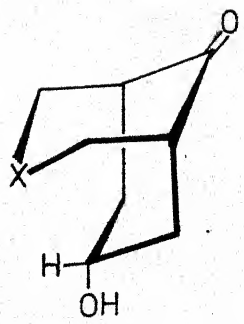
In view of the conflicting reports about the structure of the hydrate derived from 1 and absence of more recent evidence in support of the structure 4 for the hydrate from the homologous



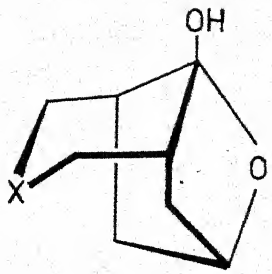
16

Scheme III.6

Reference



$NaBH_4$

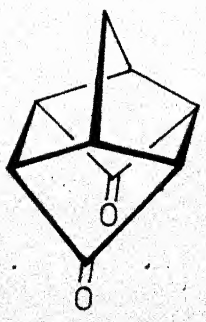


31, 32

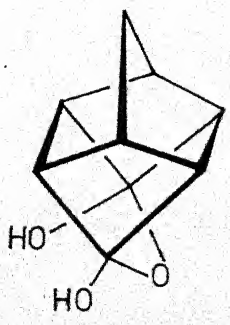
X=CH_2
X=NTs

17

18



H_3O^+



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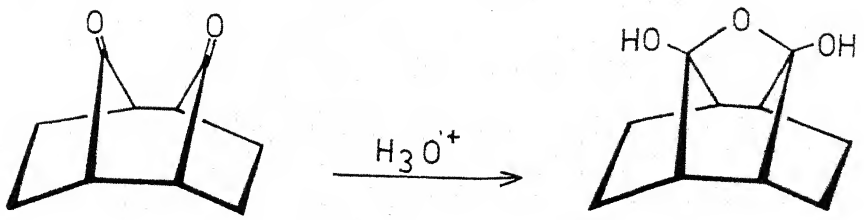
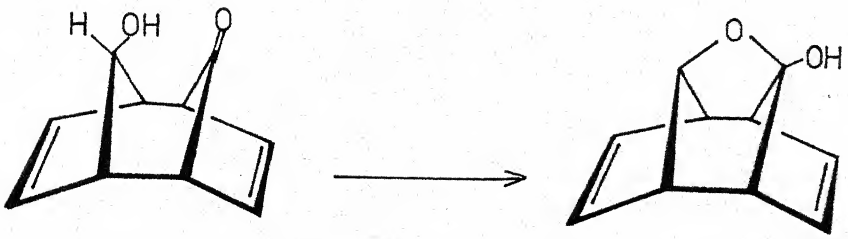
Scheme III.6 contd.

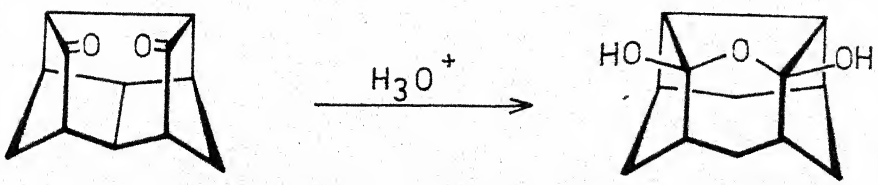
Refere



33



33



25

dione (2), it was decided to investigate the structures of these hydrates derived from 1 and 2 with the aid of modern spectroscopic methods. It became quite apparent from the beginning, in the light of the experience of previous workers [1,30] that IR and ^{1}H NMR spectroscopy cannot be very helpful in unambiguously settling the structures of the hydrates. It was therefore envisaged that ^{13}C NMR spectroscopy[34-36] could be the most appropriate and incisive technique to delineate the structures of the hydrates from 1 and 2. In order to make reliable ^{13}C NMR assignments, it was necessary to have ^{13}C chemical shift parameters for compounds bearing the skeleton of 1 and 2. Consequently, several derivatives of 1 and 2 were prepared and their ^{13}C NMR spectra were recorded to aid structural assignment of the hydrates. It will be evident that this exercise was necessary as the structure of the hydrates was crucial to the successful execution of Scheme III.1.

In this chapter of the thesis, we represent ^{13}C NMR evidence leading to unambiguous structure assignment to the hydrates derived from 1 and 2. It has been further observed that the ketol (11), contrary to earlier reports,[1,30] exists in equilibrium with its hemi-ketal form (14). Thus, for the first time pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane $\rightleftharpoons$ oxa-bird cage equilibrium has been directly observed. ^{13}C NMR chemical shifts for several derivatives of 1 and 2 have been documented, although complete assignment of all carbon resonances has not been possible. Finally, results of reaction of hydrates from 1 and 2 with lead

tetraacetate are described. Structures to various products obtained in this reaction have been elucidated and plausible mechanism is suggested for their formation.

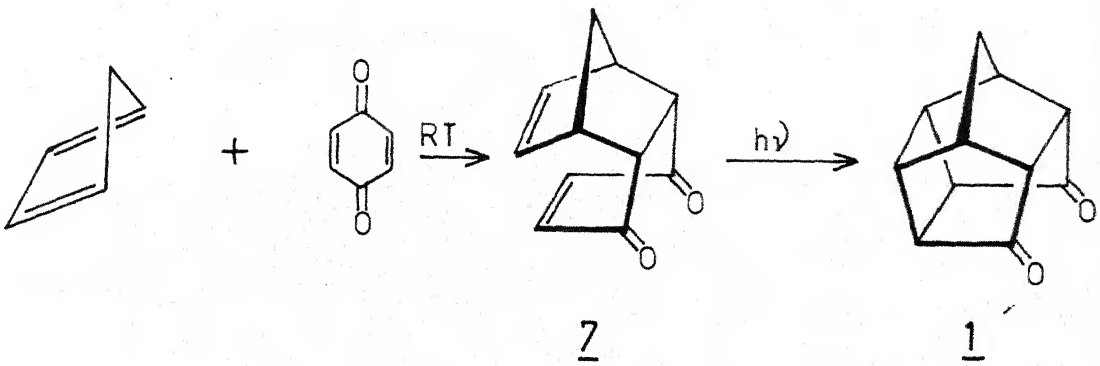
III.3 Results and Discussion

As already indicated, the first objective of this investigation was to unambiguously elucidate the structures of the hydrates derived from diones 1 and 2. These starting diones and some of their derivatives were synthesized in a straight-forward manner according to the literature procedures as depicted in Scheme III.7.

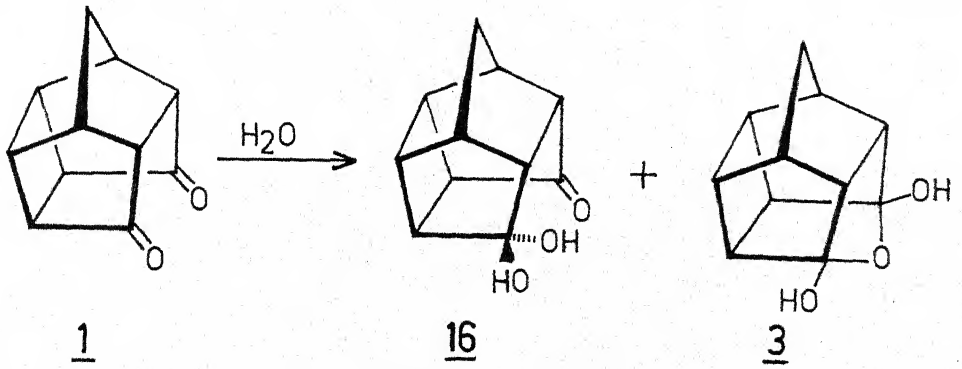
Freshly prepared and sublimed samples of diones 1, m.p.24[illegible]°C and 2, m.p. 255°C, were completely devoid of any hydrate contamination (no hydroxyl absorption in the IR spectra). As would be expected for the symmetrical structures 1 and 2, their ^{13}C NMR spectra (Fig. III.1 and III.2) showed resonances due to 6 C's each (Table III.1).

When a sample of dione (1) was either exposed to air (several weeks) or stirred in aqueous ethyl acetate for several hours (essentially the recipe used by Cookson[1] and Sasaki[30]), it showed a marked tendency towards hydration. For example, the samples of 1 recovered from air exposure or aqueous ethyl acetate treatment exhibited a broad, pronounced IR band in the hydroxyl region (3300-3500 cm^{-1}) besides the carbonyl (1750 cm^{-1}) band

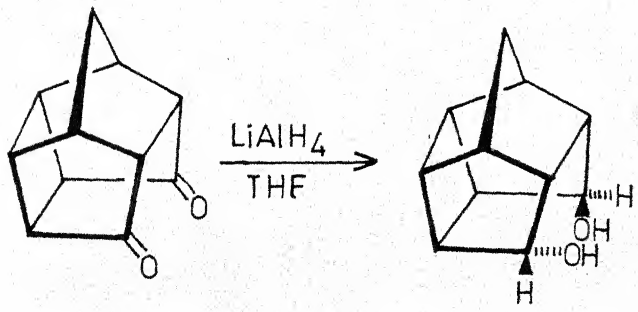
Scheme III.7



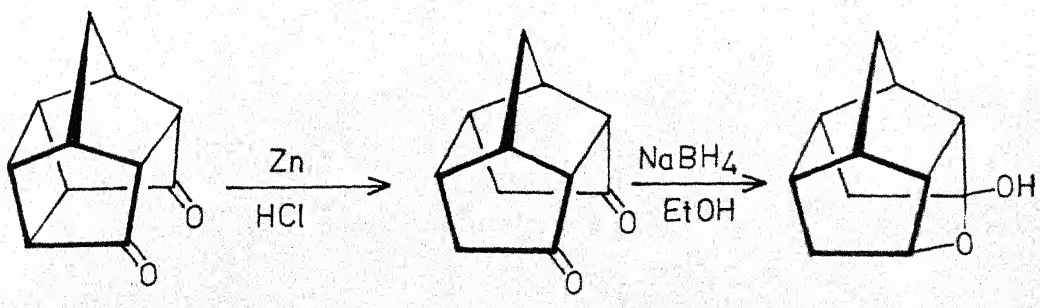
7 1



1 16 3

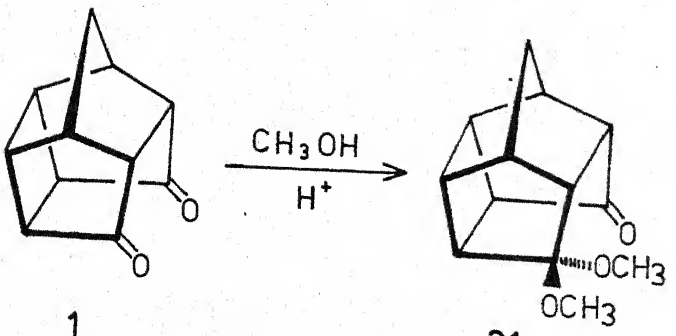


1 12

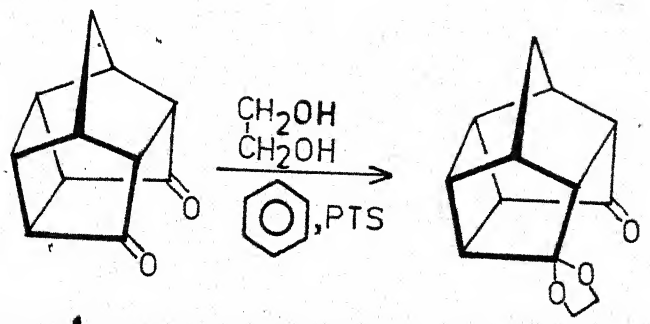


1 19 20

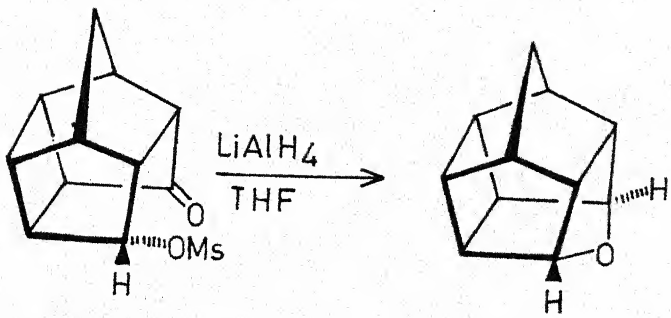
Scheme III.7 contd.



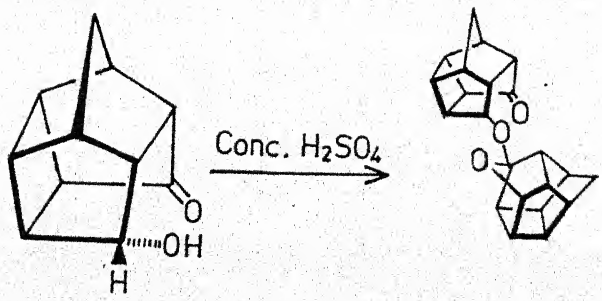
1 21



1 22

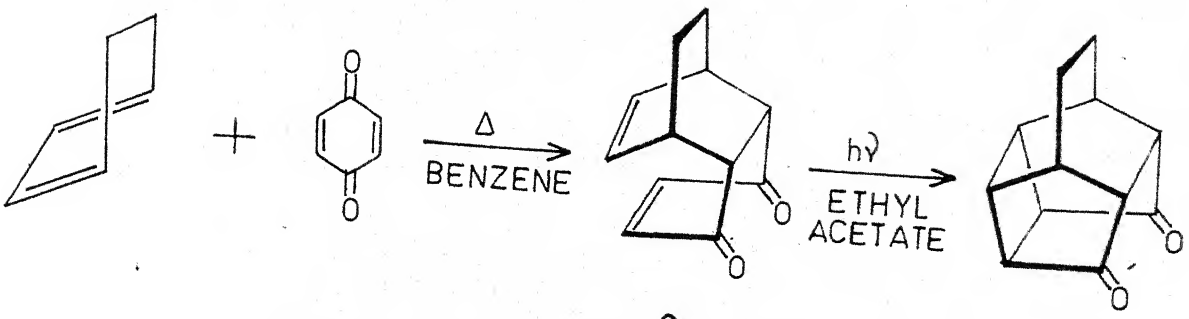


24 25

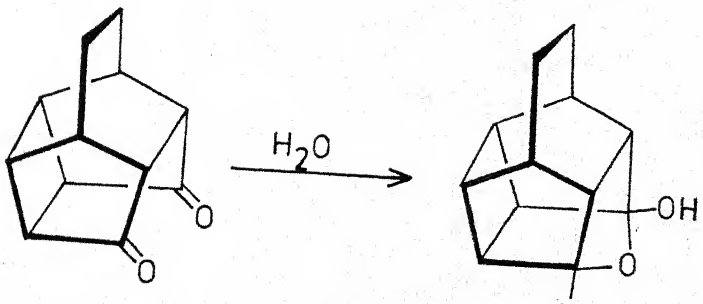


11 26

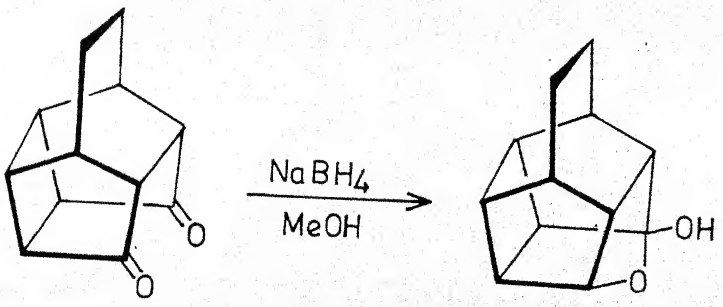
Scheme III.7 contd.



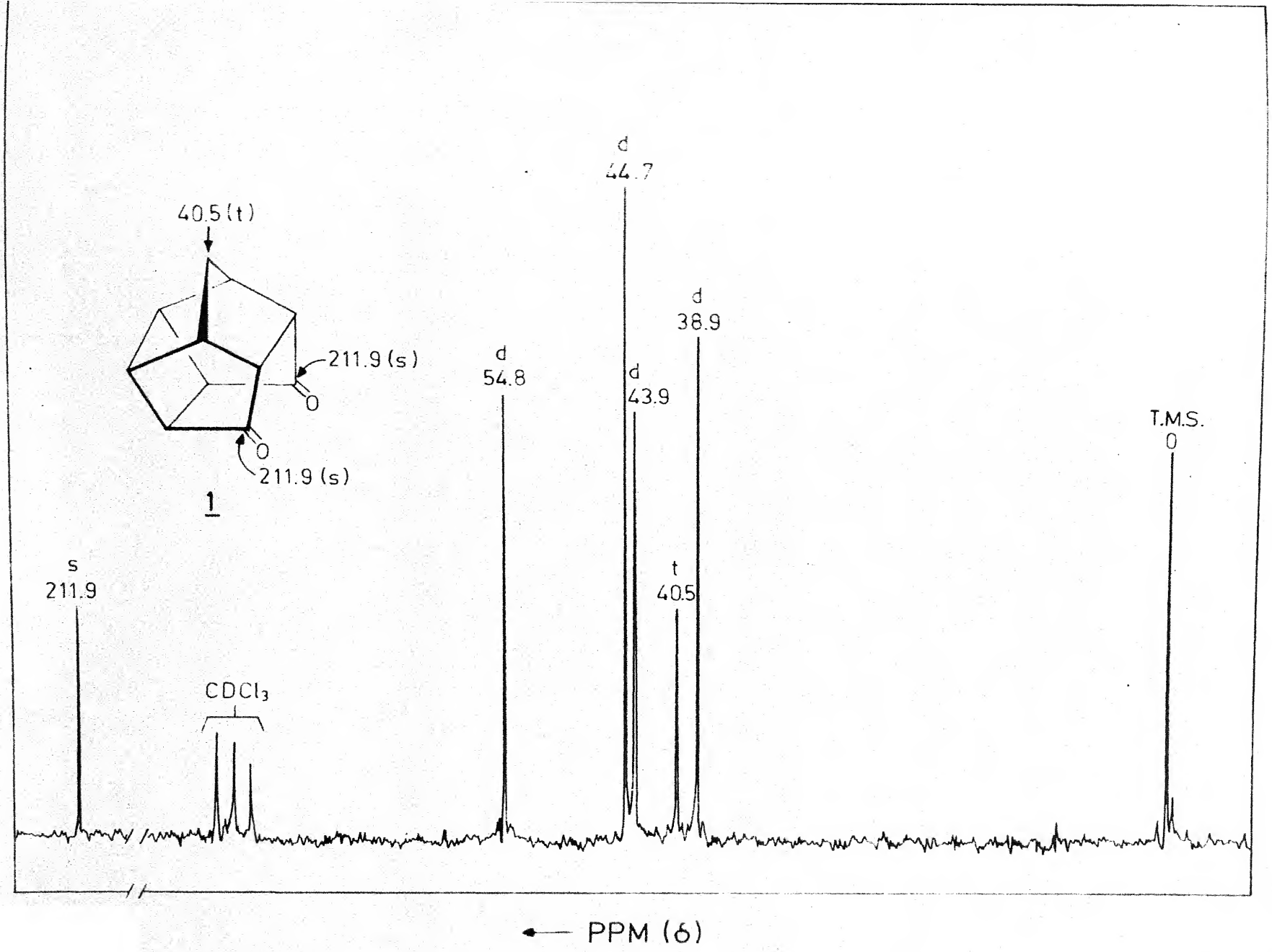
8 2



2 4



2 27



1

Fig. III.1 ^{13}C NMR spectrum (22.64MHz) of 1

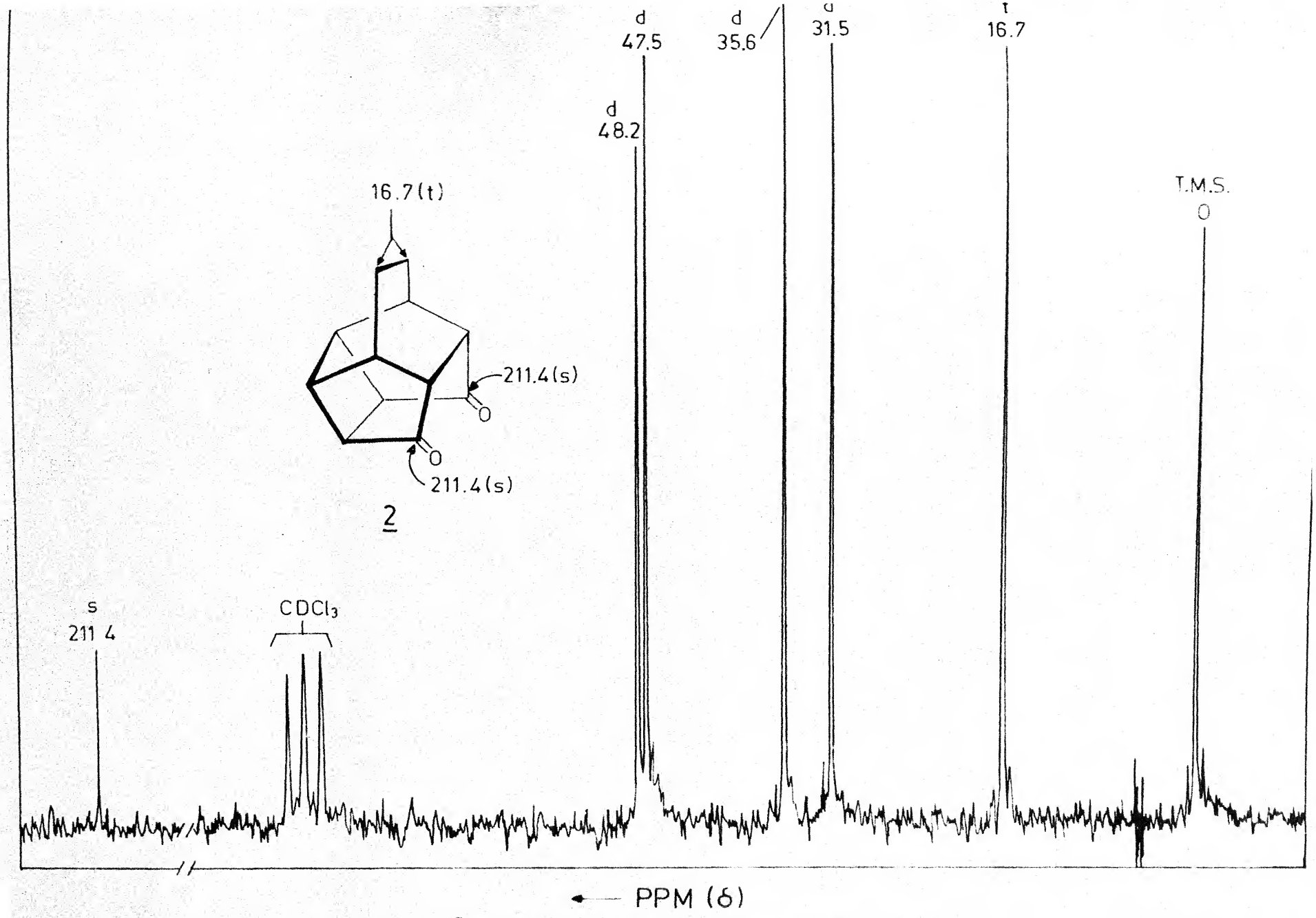
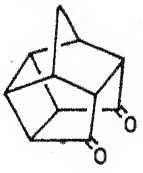
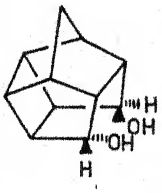
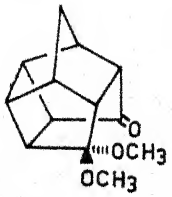
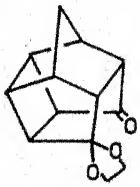
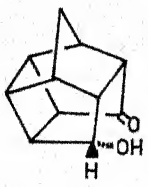
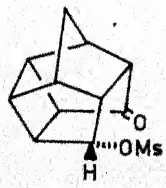
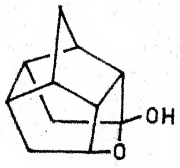
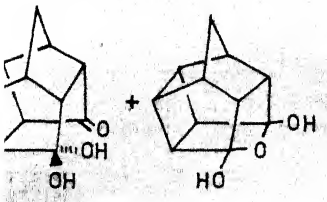
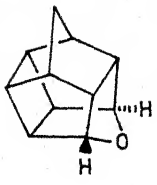
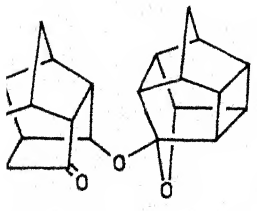
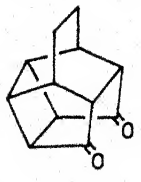
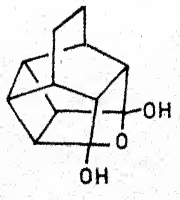
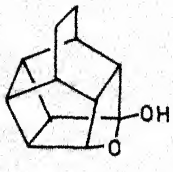


Fig. III.2 ^{13}C NMR spectrum (22.64MHz) of 2

COMPOUND	^{13}C NMR Chemical Shifts (δ)
 (1)	211.9(s), 54.8(d), 44.7(d), 43.9(d), 40.5(t), 38.9(d).
 (12)	91.5(d), 45.5(d), 42.9(d), 39.9(d), 38.3(t), 34.5(d).
 (21)	214.3(s), 107.7(s), 51.7(d), 51.1(q), 49.8(d), 48.7(q), 45.7(d), 42.9(d), 41.9(d), 41.6(d), 40.9(d), 38.4(t), 36.4(d).
 (22)	214.7(s), 114.0(s), 65.8(t), 64.6(t), 53.1(d), 50.8(d), 46.0(d), 42.9(d), 42.4(d), 41.6(d), 41.5(d), 38.8(t), 36.4(d).
 (11)	219.5(s), 119.4(s), 81.7(d), 72.2(d), 56.3(d), 55.0(d), 54.4(d), 50.0(d), 45.9(d), 45.3(?), 44.9(?), 44.8(?), 43.4(2C), 43.1, 42.2, 42.0, 41.7(2C), 40.7, 38.5(t), 37.0(d).
 (24)	214.9(s), 78.1(d), 51.2(d), 49.9(d), 44.2(d), 42.1(2C, d), 40.7(d), 40.5(d), 38.4(q), 38.3(t), 37.0(d).

 (20)	115.7(s), 81.1(d), 58.7(d), 53.9(d), 49.4(d), 47.6(d), 43.7(t), 42.3(d), 41.4(d), 38.1(t), 37.9(t).
 (16 + 3)	217.2(s), 116.3, 104.8(s), 55.7(d), 54.4, 50.6(d), 46.8(d), 44.6(d), 43.5(d), 43.3, 42.9, 42.4(d), 41.7, 41.5(d), 38.8(t), 36.4(d).
 (25)	85.8(d), 54.5(d), 44.0(d), 42.0(t), 43.7(d), 41.6(d).
 (26)	215.8(s), 122.1(s), 81.5(d), 75.3(d), 54.6(d), 53.7(2C, ?), 52.6(d), 50.2(d), 45.2(d), 44.4(?), 44.2(?), 43.5(?), 42.9(?), 42.0(?), 41.7(2C, d?), 40.9(d), 38.4(t), 37.0(d).
 (2)	211.4(s), 48.2(d), 47.5(d), 35.6(d), 31.5(d), 16.7(t).
 (4)	110.5(s), 48.7(d), 48.5(d), 37.0(d), 31.2(d), 17.2(t).
 (27)	118.0(s), 79.9(d), 47.9(d), 47.2(d), 45.5(d), 37.7(d), 37.2(d), 32.7(d), 30.5(d), 17.6(t), 17.2(t).

whose intensity was weaker than in the starting dione. The tlc behaviour of the hydrated 1 indicated it to be a mixture, as the sharp, crisp spot of 1 now looked diffused and elongated. On heating to 150°C or sublimation, the hydrated product lost water and the starting dione was quantitatively recovered. On the basis of this evidence (particularly IR) the hydrated product could be either 16 or a mixture of 1 and the dihydroxy ether (3). The ^{1}H NMR spectrum of the hydrated dione was not particularly informative as it resembled the starting dione and only some minor shifts and broadening of resonances was discernible. However, a careful analysis of ^{13}C NMR spectrum (Fig. III.3) clearly revealed the nature of the hydrate derived from 1 and its constituents could be identified though characteristic carbon shieldings. For example, the ^{13}C NMR spectrum showed a doubled set of resonances, one set with higher intensities and the other set having weaker but clearly discernible signals. The dominant set of signals* at δ 217.2(s), 104.8(s), 55.7(d), 50.6(d), 46.8(d), 43.5(d), 42.4(d), 41.5(d), 38.8(t), 36.4(d) indicated the unsymmetrical nature of the product and could be readily assigned to the structure (16). Besides the carbonyl carbon at δ 217.2(s), the singlet signal due to quarternary carbon attached to two oxygens ($>C<^{OH}_{OH}$) at δ 104.8(s) was of much diagnostic value. The appearance of the methylene carbon at δ 38.8(t) gave assurance that no skeletal changes in the molecule had occurred

*Off-resonance multiplicities are given in parentheses. The operating conditions for recording the ^{13}C NMR spectra are given in the experimental section of this chapter.

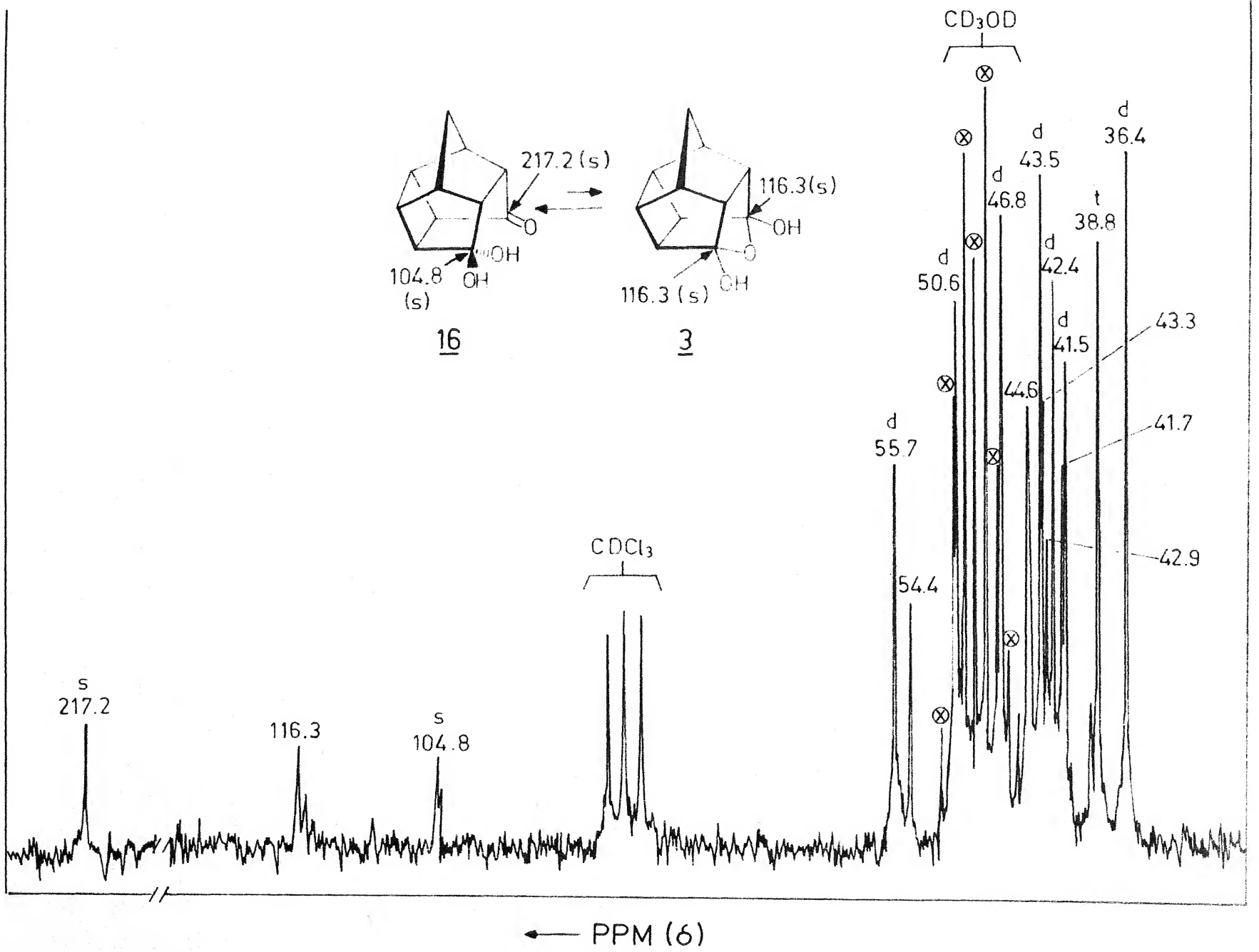


Fig.Ⅲ.3 ^{13}C NMR spectrum (22.64MHz) of the mixture of 3 + 16

during the hydration. A perusal of Table III.1 will reveal that the carbon resonance of the methylene group, easily identifiable due to its multiplicity in off-resonance spectrum, is very typical of the pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane ring system. The minor resonances* (Fig. III.3) in the ^{13}C NMR spectrum of the hydrate at δ 116.3, 54.4, 44.6, 43.3, 42.9 and 41.7 could be at once attributed to the contribution of the dihydroxy ether form 3 bearing the oxa-bird cage framework. The carbon signal at δ 116.3 is very characteristic (see Table III.1 and *vide infra*) and could be assigned to the carbon attached to hydroxy-ether functionality ($>C\begin{matrix}OH\\O-\end{matrix}$). The other resonances at δ 54.4, 44.6, 43.3, 42.9 and 41.7 compared favourably with the carbon chemical shifts (Table III.1) of parent oxa-bird cage compound 25 which appeared at δ 54.5, 44.0, 43.9, 43.7 and 41.6. Furthermore, no additional resonance at δ ~38.5 due to the methylene carbon of the pentacyclic system was present. Thus, an equilibrium between the pentacyclic form and the oxa-bird cage form in the hydrate derived from dione (1) was firmly indicated.

More convincing evidence to support the above assignments was forthcoming from the ^{13}C NMR spectrum of the hydrate derived from dione (2). The diketone (2) was readily hydrated on short exposure to air (long gestation period of 18 months was not

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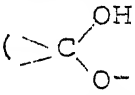
*Due to weak intensity of this set of signals and overlap with other signals, the off-resonance multiplicities could not be ascertained reliably.

necessary) and the insoluble hydrate, m.p. 252-3°C, on sublimation regenerated the diketone (2). This hydrate was devoid of any carbonyl absorption in the IR spectrum, and its ^{13}C NMR spectrum (Fig. III.4) exhibited, as expected of a symmetrical structure, six resonances of δ 110.5(s), 48.7(d), 48.5(d), 37.0(d), 31.2(d), 17.2(t). Compared with the starting dione (2) (Table III.1), one can notice the disappearance of the carbonyl carbon signal at δ 211.4 and emergence of a quarternary carbon singlet at δ 110.5 due to a carbon attached to the hydroxy-ether functionality (). This feature not only confirms the structure of the hydrate (4) derived from 2 but lends credibility to the assignment of minor resonances in the hydrate from dione (1) to the dihydroxy-ether form (3).

Having established the existence of oxa-bird cage form (3) in the hydrate derived from 1, it was of interest to further probe this type of equilibrium and consequently the ^{13}C NMR spectrum of the known ketol (11), m.p. 270-1°C, prepared according to literature procedure, was examined. Initially, even a casual examination of the IR spectrum of 11 aroused some suspicion in our mind because of its somewhat low intensity carbonyl band. However, the ^{1}H NMR spectrum (Fig. III.5) of ketol (11), to our surprise showed two low-field protons at δ 4.59 (t, J = 5 Hz) and 4.07 (t, J = 4 Hz) due to protons attached to carbon having oxygen in different enviornment. Furthermore, the integration of the two singnals showed them to

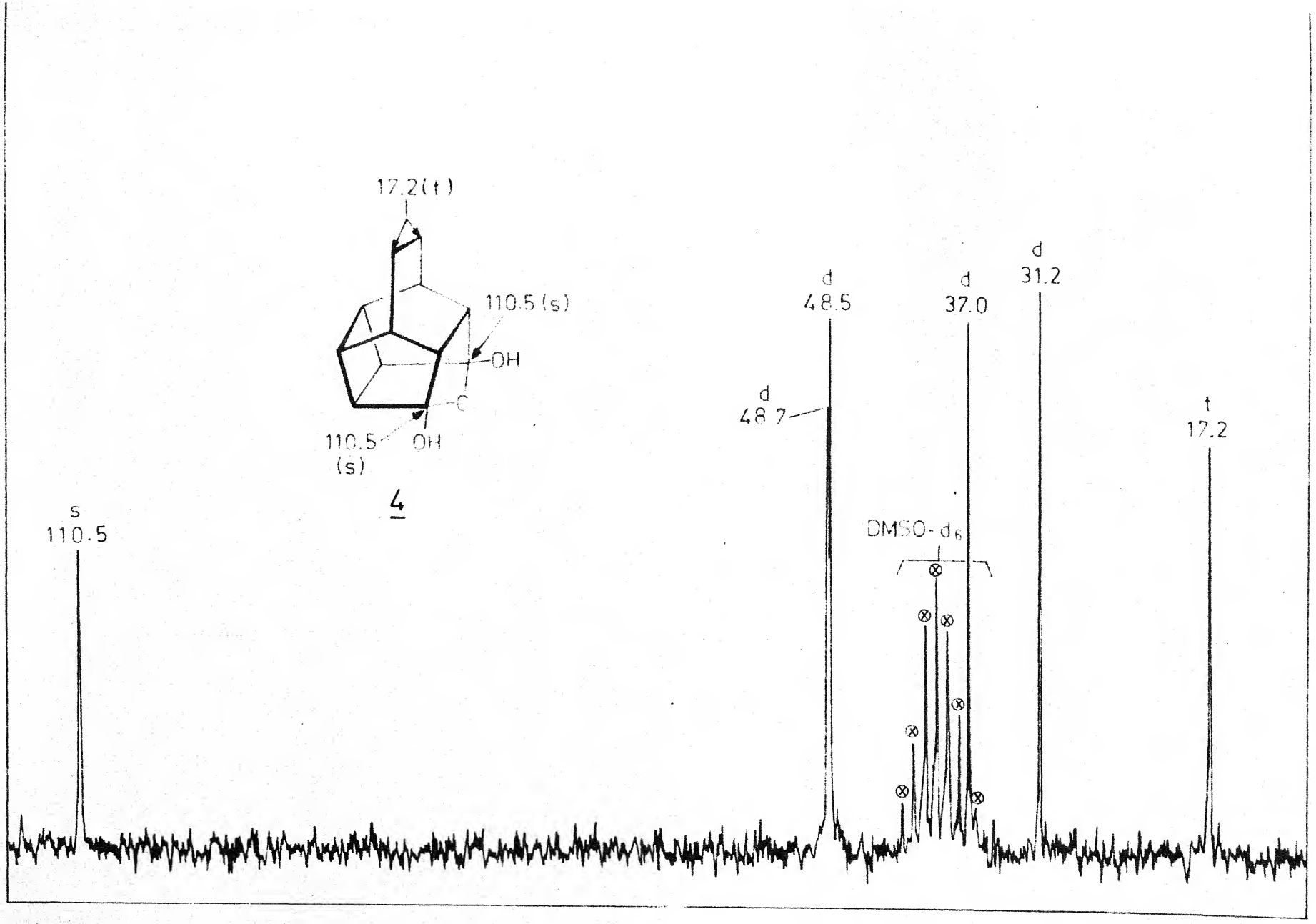


Fig.Ⅲ.4 ^{13}C NMR spectrum (22.64MHz) of 4

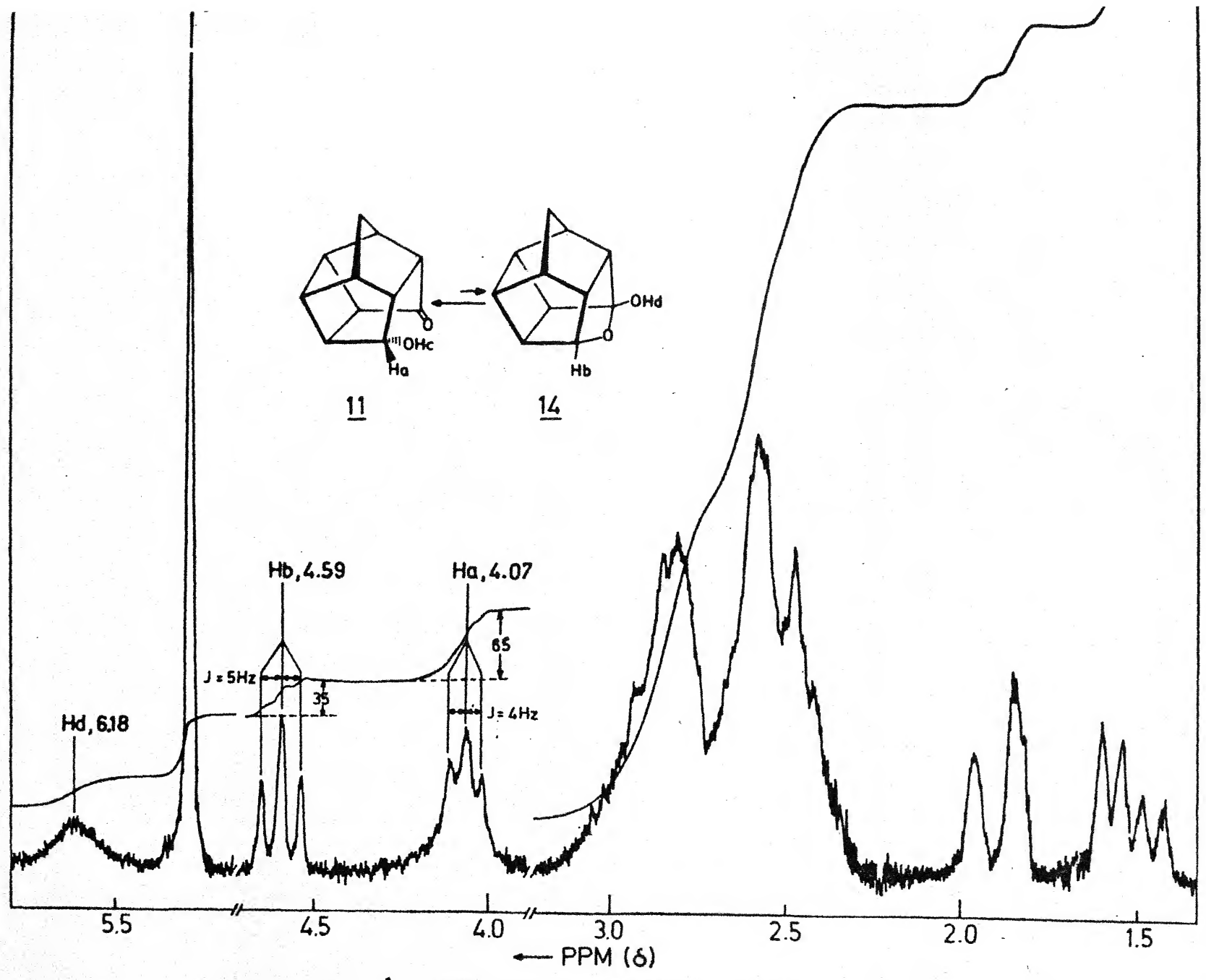


Fig.III.5 ^{1}H NMR spectrum (90MHz) of 11 + 14

have a relative ratio of 35:65, respectively.* The ^{13}C NMR spectrum (Fig. III.6) of this ketol showed a doubled set of resonances due to 22 C's and the presence of open 11 and the cyclic hemi-acetal form 14 were discernible. Thus, characteristic signals at δ 219.5 (s, carbonyl C), 72.2 (d, hydroxyl bearing C) and 38.5 (t, methylene C) could be readily assigned to the hydroxy-ketone form 11. On the other hand resonances at δ 81.7 (d) and 119.4 (s) were characteristic of the carbon attached to oxygen in the oxa-bird cage system (cf. δ 85.8 for 25) and carbon attached to the hemi-ketal functionality (cf. 20 & 27 ^{13}C chemical shifts, Table III.1). Therefore, it became quite apparent that the previously described ketol in fact is an equilibrium mixture of 11 and 14.

A comparison here with the homologous series corresponding to dione (2) will be in order. Sodium borohydride reduction of dione (2, Scheme III.8) furnished a crystalline product, m.p. 238-239°C, which was devoid of carbonyl absorption and showed only strong hydroxyl absorption in the IR spectrum. The ^{1}H NMR spectrum and ^{13}C NMR spectrum (Fig. III.7 and Table III.1) revealed its cyclic hemi-ketal structure 27. The chemical shifts of the oxygen bearing carbons of δ 118.0 and 79.9 further supported the existence of oxa-bird cage form in the ketol obtained from 1.

Addition of a few drops of trifluoroacetic acid (TFA) to the equilibrium mixture 11 ⇌ 14 resulted in the coalescence of

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*Ketol (9) could not be resolved either by GLC or HPLC (μ-Porasil column).

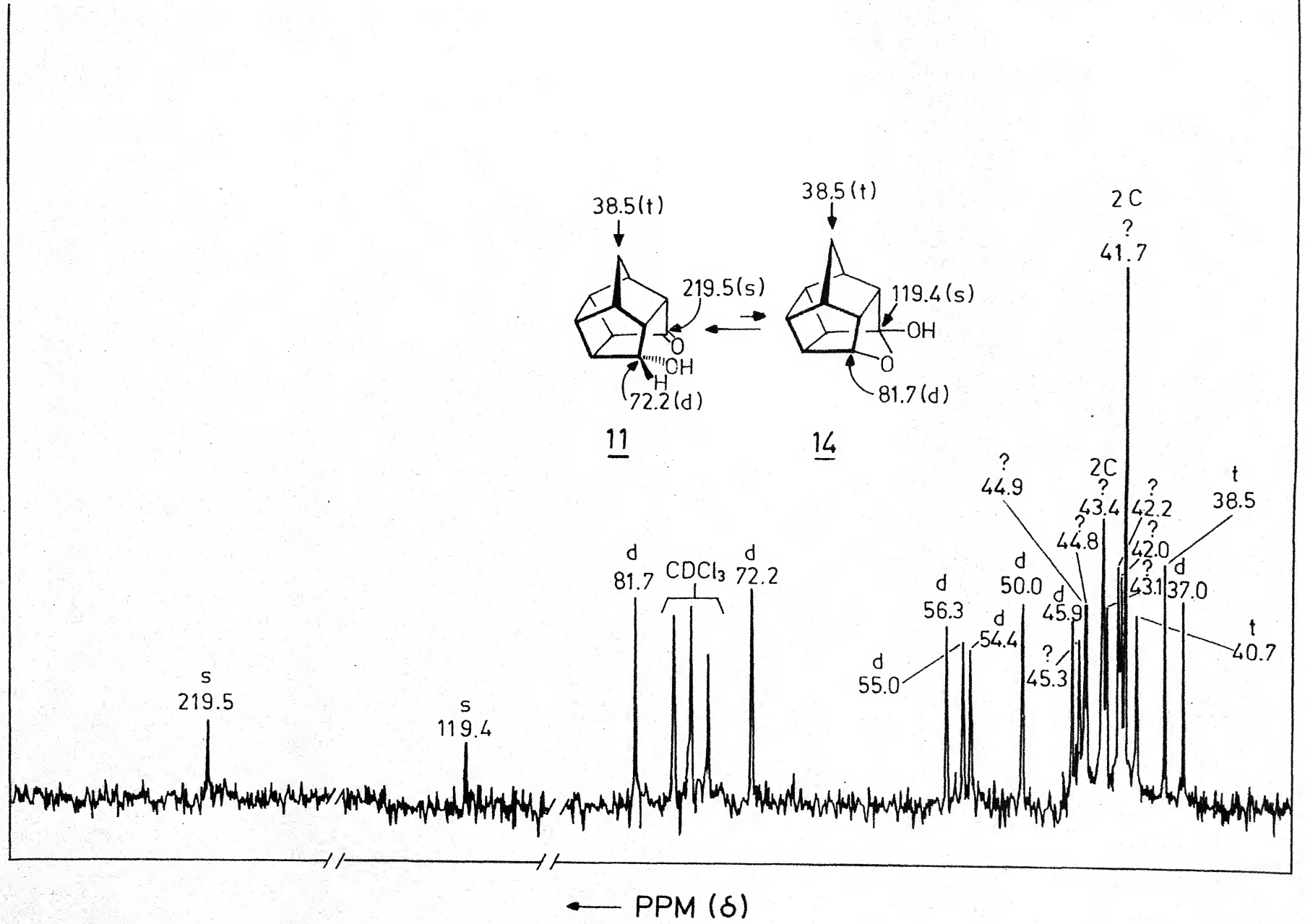
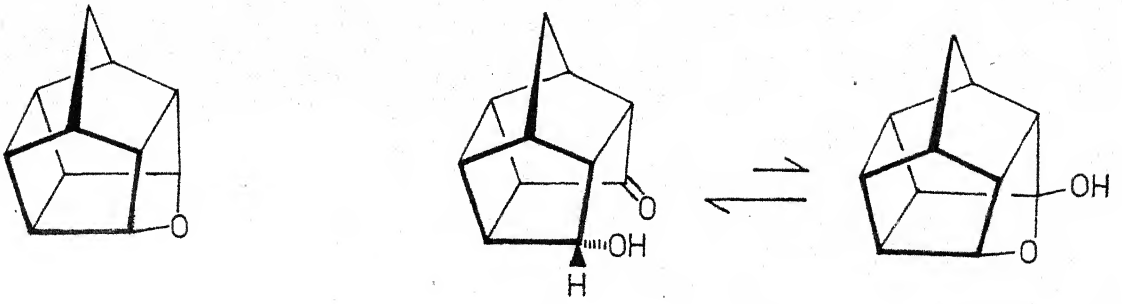
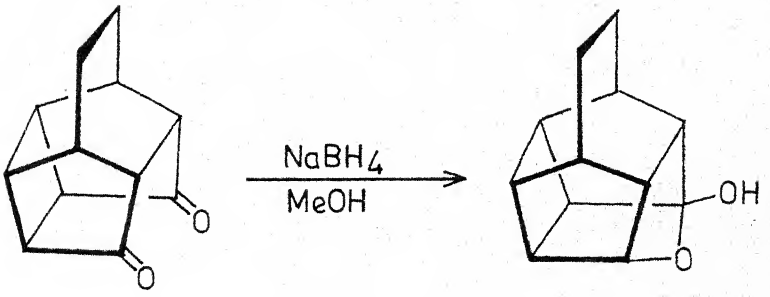


Fig.Ⅲ.6 ^{13}C NMR spectrum (22.64MHz) of 11 + 14



25 11 14

Scheme III.8



2 27

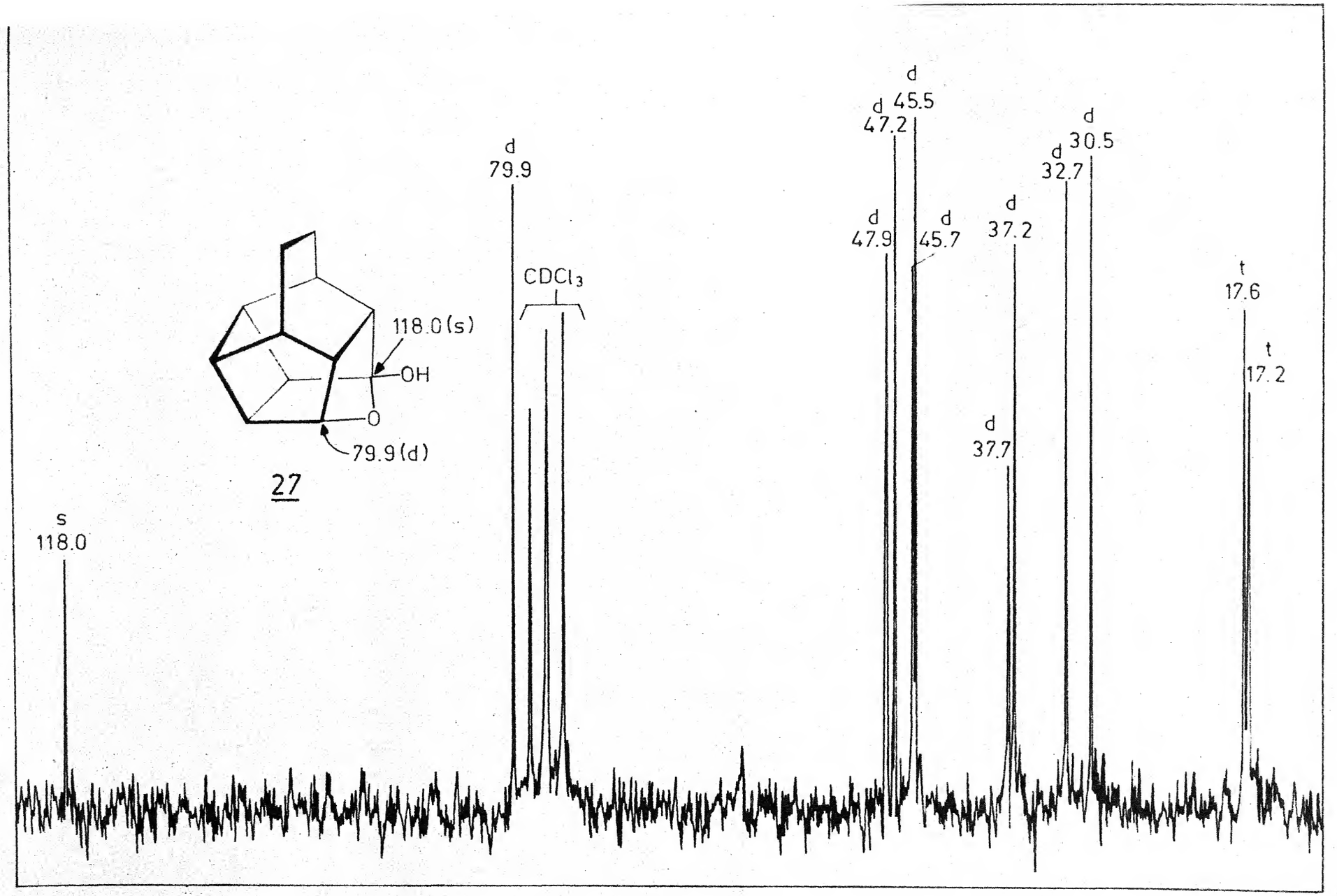


Fig. Ⅲ.7 ^{13}C NMR spectrum of (22.64MHz) 27

^{13}C NMR lines and a spectrum (Fig. III.8) showing eleven lines (δ 179.7, 76.3, 54.6, 52.6, 45.1, 43.9, 42.9, 42.6, 41.6, 40.6, 39.2) with absorptions in between the original positions in 11 and 14 were obtained. For example, the carbon resonance at δ 179.7 was an average between the carbonyl carbon in 11 at δ 219.5 and the hemi-ketal function bearing carbon in 14 at δ 119.4. This spectrum therefore seems to represent an average between 11 and 14 caused by fast interconversion in a dynamic equilibrium between the pentacyclic and the oxa-bird cage form.

In the present case, therefore, ^{13}C NMR spectroscopy provides new, direct and otherwise inaccessible clue to the existence of pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane $\rightleftharpoons$ oxa-bird cage equilibrium. After the completion of our studies, Speckamp and coworkers[37,38] have described the study of similar type of equilibrium in the bicyclo(3.3.1)nonane system (Scheme III.9) with the aid of ^{13}C NMR spectroscopy.

With the structures of the hydrates devised from 1 and 2 firmly established as an equilibrium mixture of 3 + 16 and 4, respectively, their reaction with LTA was investigated as envisaged in Scheme III.1. However, it became evident to us at this stage that with very small concentration of dihydroxy-ether 3 present in the hydrate derived from dione (1), the chance of accomplishing the contemplated fragmentation (Scheme III.1) in this case would not be too encouraging.

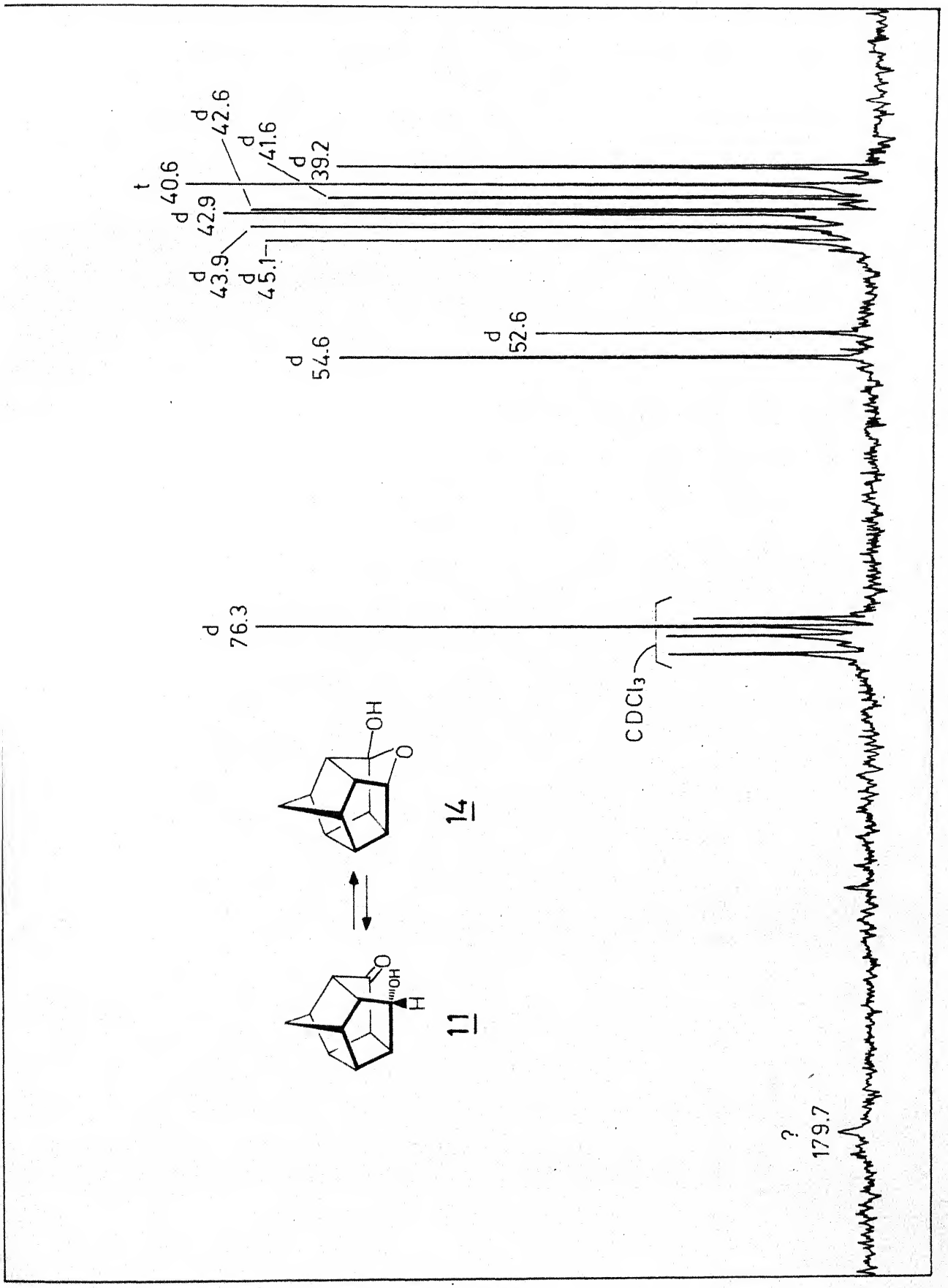
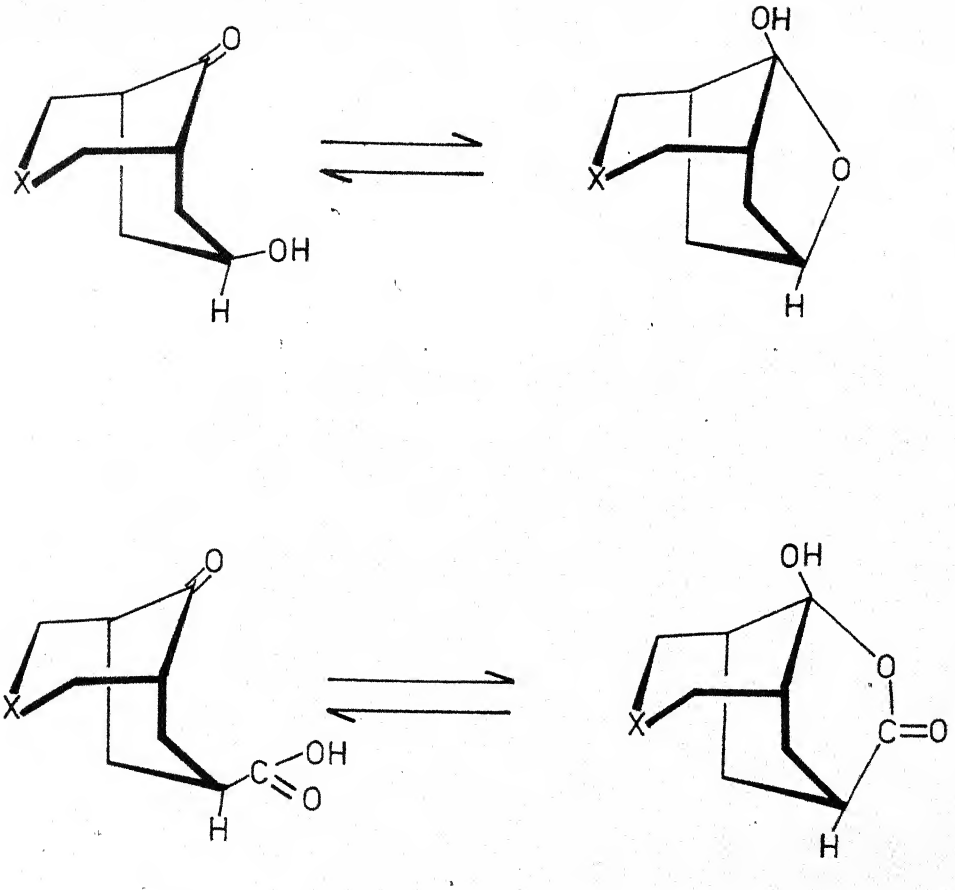


Fig.III.8 ^{13}C NMR spectrum (22.64MHz) of 11 + 14 in TFA

Scheme III.9



X = CH_2

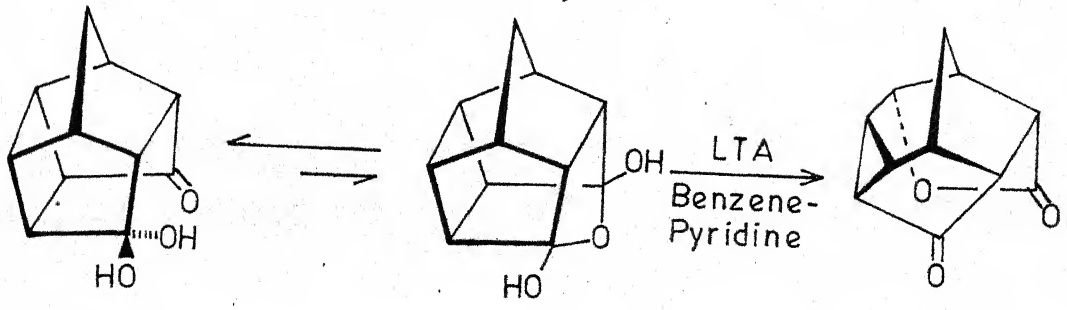
X = NTs

Reaction of hydrate 3 + 16 from dione (1), with LTA in refluxing benzene-pyridine for six hours resulted in the isolation of a single crystalline solid, m.p. 280°C in nearly 80% yield (Scheme III.10). This compound exhibited IR bands at 1780 cm^{-1} (strained δ-lactone) and 1725 cm^{-1} (cyclopropyl conjugated to a five-membered ketone) and its ^{1}H NMR and ^{13}C NMR spectra revealed its identity with 28, a product obtained previously in our laboratories[39] *via* ceric ion oxidation of dione (1).

Formation of 28 from 16 during LTA reaction could be rationalized *via* a straight-forward mechanism depicted in Scheme III.11, which involves heterolytic fragmentation of the Pb^{IV} ester, a cyclobutyl → cyclopropylcarbinyl carbonium ion rearrangement and intramolecular lactonization. Results described in Chapter II of this thesis provide adequate procedence for the facile carbonium ion rearrangement encountered here.

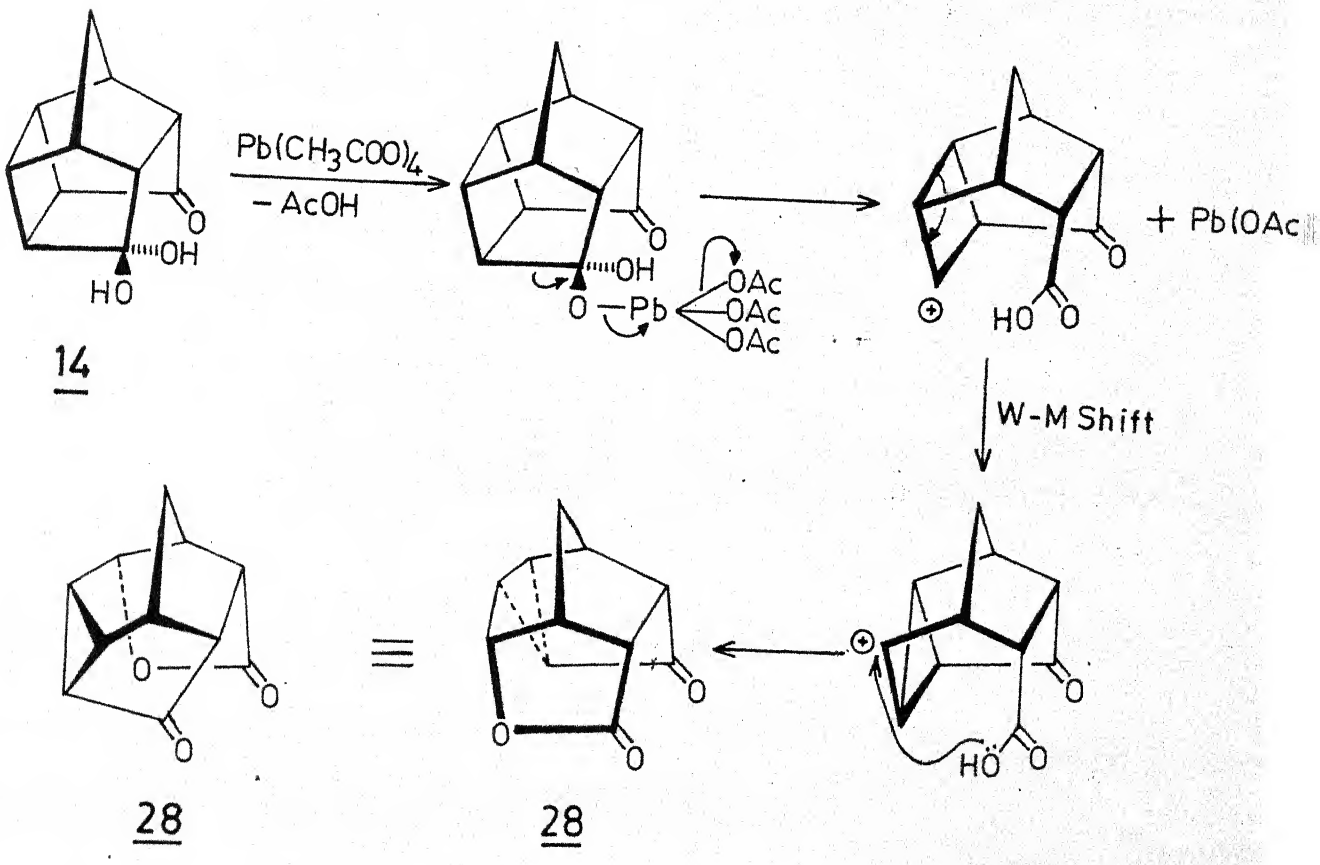
The transannular hydrate (4) on reaction with LTA in refluxing benzene-pyridine for 8 hr furnished two products in 25% and 20% yield. Separation of these two polar products was achieved *via* column chromatography on silica-gel. The less polar product, m.p. 199°C, $C_{12}H_{12}O_3$, was quickly recognized as the expected anhydride 29, and its structure follows from the evidence summarized below. The IR spectrum exhibited characteristic anhydride bands at 1780, 1840 and 1860 cm^{-1}. The ^{1}H NMR spectrum (Fig. III.9) showed two olefinic protons at δ 6.13(s)

Scheme III.10



16 3 28

Scheme III.11



14

28 ≡ 28

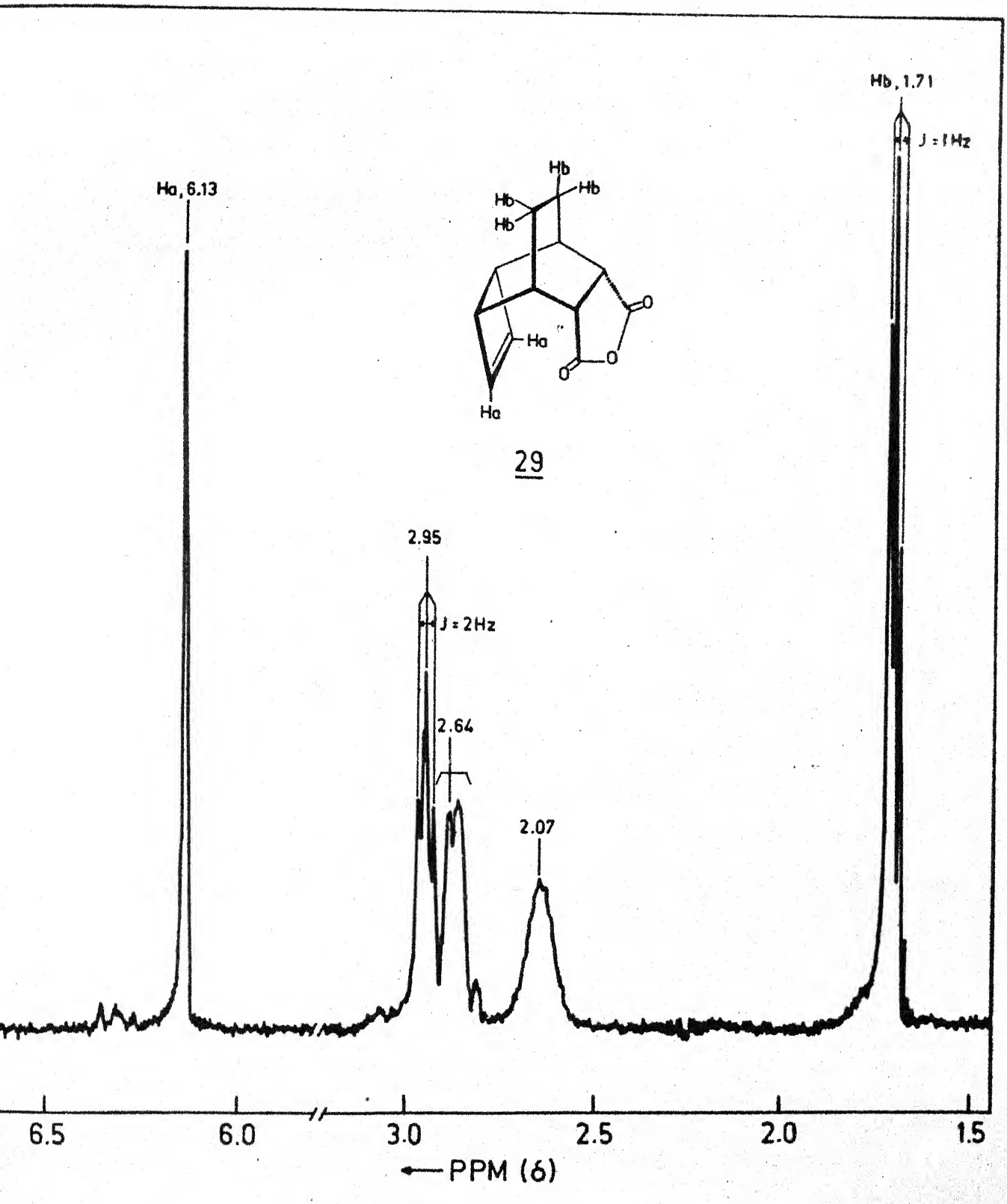
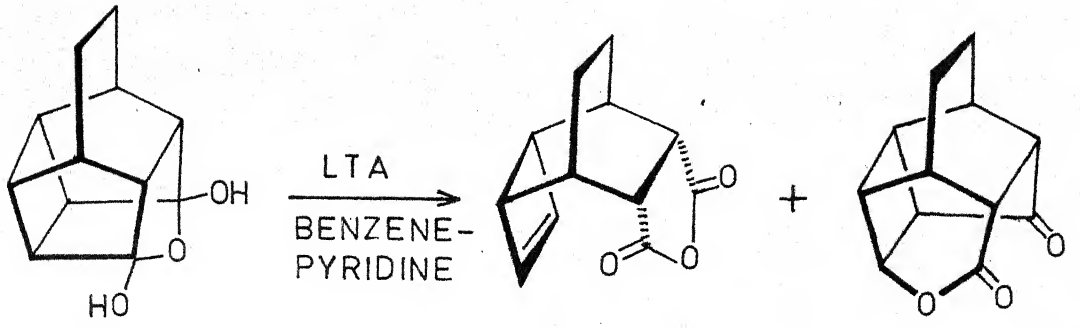


Fig. Ⅲ.9 ^{1}H NMR spectrum (90MHz) of 29

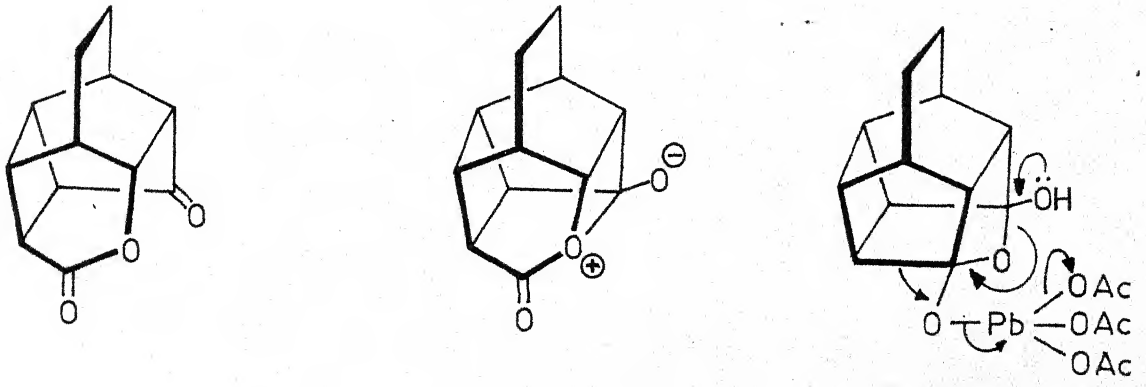
besides resonances at δ 2.64 (2H, br, ring CH), 2.07 (2H, m, ring CH), 2.95 (2H, t, J= 2 Hz, ring CH), and 1.71 (4H, t, J=1Hz, $-CH_2-CH_2-$). These spectral features revealed the symmetrical nature of the anhydride 29 (Scheme III.12) which were further confirmed by the six lines in the ^{13}C NMR spectrum (Fig. III.10). Two characteristic carbon resonances at δ 174.7(s) and 142.7(d) were assigned to the anhydride carbonyl and cyclobutene olefinic carbons.

The polar component from the LTA reaction of 4 is tentatively assigned the tetracyclic lactone structure 30 (Scheme III.12), m.p. 274-6°C, $C_{12}H_{12}O_3$, on the basis of its spectral properties. The IR absorptions at 1735 and 1750 cm^{-1} in 30 could be attributed to the five-membered ketone and the δ-lactone functionality. The ^1H NMR spectrum (Fig. III.11) showed the presence of a low-field proton attached to lactone oxygen at δ 4.83 (dt, J_1= 3 Hz, J_2= 10 Hz). The rest of the signals in the proton spectra consisted of several multiplets between δ 1.76 and 3.63 due to the rest of the ring protons. The ^{13}C NMR spectrum (Fig. III.12) exhibited resonances due to a carbonyl carbon (δ 171.9, s) and carbon attached to lactone oxygen (δ 77.3, d) besides signals at δ 53.4 (d), 46.6(d), 39.8(d), 34.4(d), 33.9(d), 31.7(d), 29.6(d), 19.6(t) and 16.7(t). Although, this data cannot conclusively rule out the regioisomeric lactone structure 31, we prefer formulation 30 on the basis of several considerations. Main among them is the similarity of chemical shifts of carbonyl carbons (δ 210.8 and

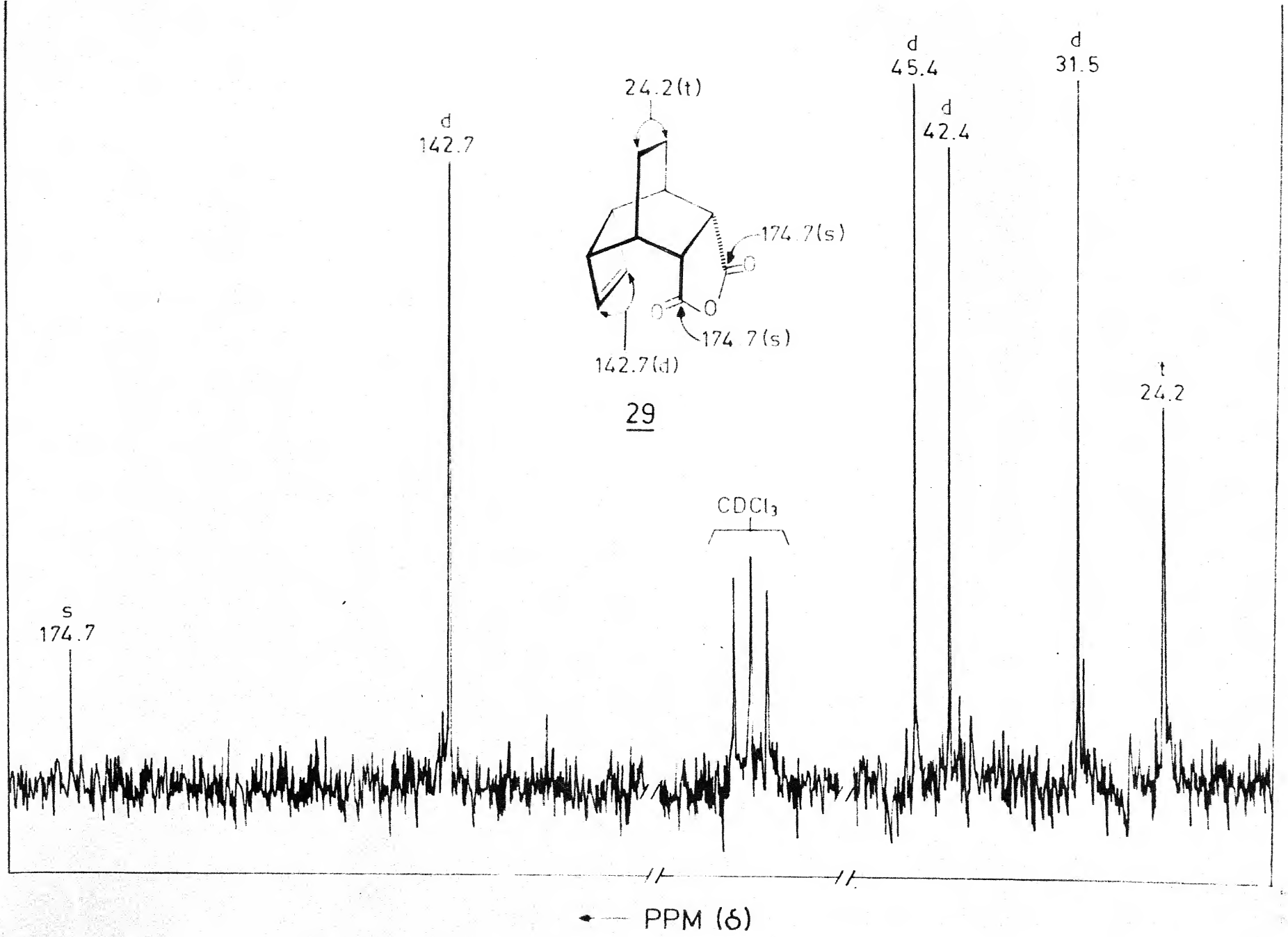
Scheme III.12



4 29 30



31 32 33



29

Fig.Ⅲ.10 ^{13}C NMR spectrum (22.64MHz) of 29

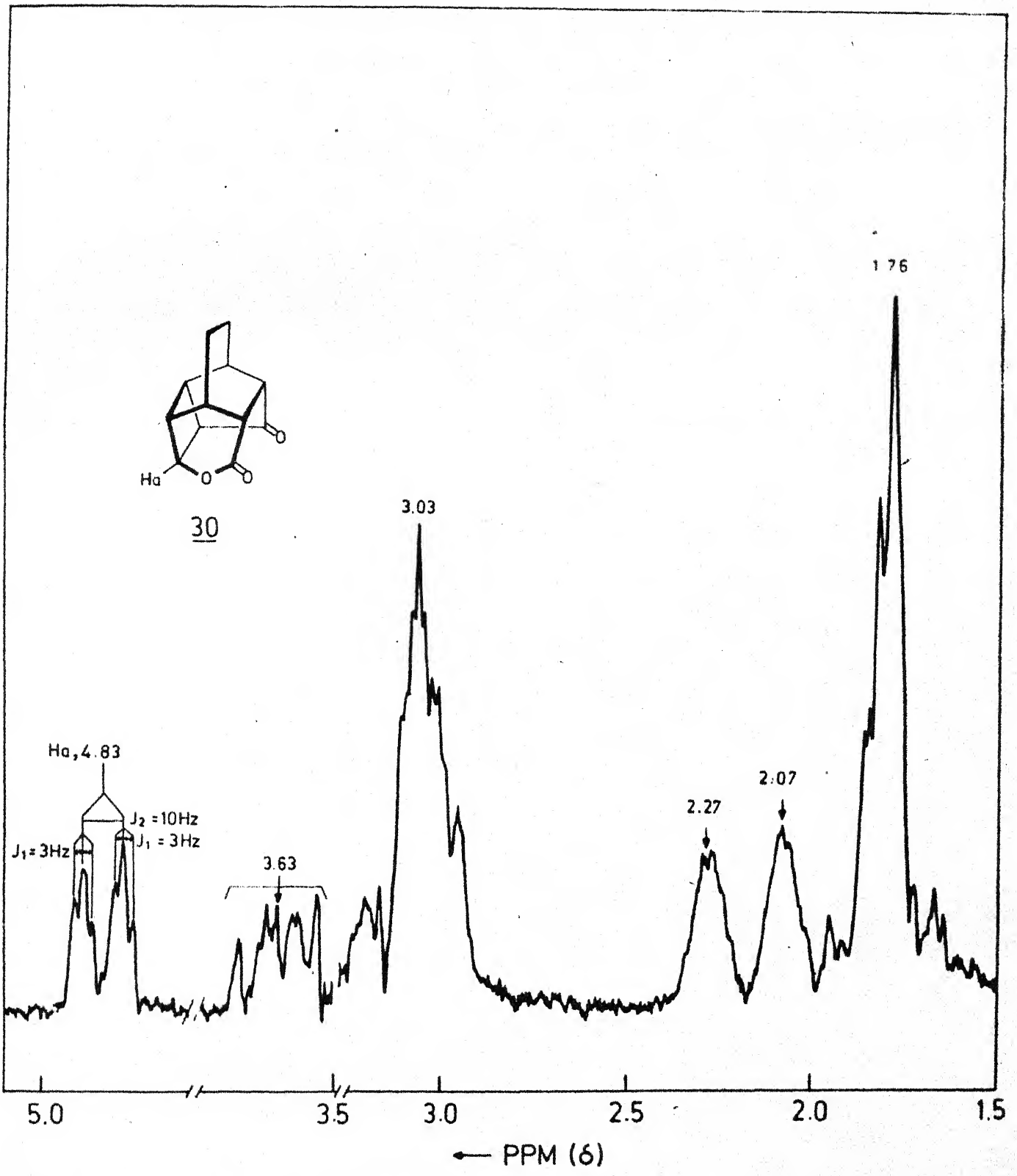


Fig.Ⅲ.11 ^{1}H NMR spectrum (90MHz) of 30

211.4) in 30 and dione (2), respectively. The alternate structure 31 is expected to have some contribution from the dipolar form 32 and would significantly alter the carbonyl carbon shielding in the ^{13}C NMR spectrum compared to 2, which we have not encountered. We have observed such shifts in carbonyl carbon resonance of polycyclic ketones due to suitably placed transannular oxygen atoms. Mechanistically, the formation of lactone 30 from 4 could be rationalized as proceeding via an intermediate like 33.

Although, we succeeded in preparing the required anhydride 29, its yields were rather unsatisfactory from preparative point of view. Several variations in reaction conditions and even change to ceric(IV) as the reagent for fragmentation did not materially increase the yield of 29. In view of this, we did not proceed further along Scheme III.1, inspite of having obtained the requisite precursor 29 from the dione (2) in only two steps.

III.4 EXPERIMENTAL SECTION

All ^{13}C NMR spectra were recorded on a Bruker WH-90 spectrometer operating at 22.6464 MHz in the F-T mode. All samples were run in $CDCl_3$ if not otherwise noted. The sweep range in all cases was 6024 Hz and the pulse frequency was 11990 Hz. The number of scans usually varied between 2000-5000

and the time between two pulses was 9.7 sec. The pulse duration was 3.5 microsec. in all cases giving a flip angle of about 20°. All chemical shifts are given with respect to TMS, and the centre lines of the solvents' signals agree with those reported in literature (77.1 ppm for $CDCl_3$). The numbers on the top of each peak in the ^{13}C NMR figures are the chemical shifts. The letters represent the multiplicities of the corresponding signals in the "off-resonance" spectra (s = singlet, quarternary carbon; d = doublet, methine carbon; t = triplet, methylene carbon; q = quartet, methyl carbon). If the multiplicity could not be determined unambiguously, a question mark is written.

Cyclopentadiene-p-benzoquinone adduct (7)

To an ice-cold solution of freshly sublimed p-benzoquinone (20 g, 0.18 mol) in dry benzene (50 ml) was added freshly distilled cyclopentadiene (12.3 g, 0.18 mol) with gentle swirling of the flask. After the addition was complete, the reaction flask was left aside at room temperature for 2 hr for crystallization. Filtration gave 28 g (88%) of the adduct (7) as pale yellow crystals, mp 76° (lit.[40] 75-76°C).

IR spectrum (KBr), ν_{max}: 1670 (carbonyl), 835 and 750 cm^{-1}.

^1H NMR spectrum (60 MHz, $CDCl_3$): δ1.4($-C\underline{H}_2$, 2H, s), 3.12 and 3.14 (C-H ring, 4 H, pair of s), 5.94 (H-C=C-H, 2H, s), 6.4 (O=C-CH=CH-C=O, 2H, s).

Pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione (1)

A solution of the adduct (7, 15 g, 0.086 mol) in ethyl acetate (200 ml) was purged with a slow stream of purified nitrogen for 25 min. The solution was then irradiated with a 450 W Hanovia medium pressure mercury arc lamp for 7 hr in a pyrex immersion well. Removal of solvent and direct crystallization from benzene-petroleum ether mixture furnished stout, white crystals of diketone (1). The yield was 13 g (87%), mp 243-244° (lit.[1] 245°C). This sample was twice sublimed at 150°C/2 mm.

IR spectrum (KBr), ν_{max}: 1750 cm^{-1} (carbonyl).

^{1}H NMR spectrum (90 MHz, $CDCl_3$): δ 1.7 (-C<u>H</u>$_2$, 2 H, centre of AB quartet, J = 10 Hz), 2.2-3.0 (C-<u>H</u> ring, 8 H, en).

^{13}C NMR spectrum ($CDCl_3$): δ 211.9(s), 54.8(d), 44.7(d), 43.9(d), 40.5(t), 38.9(d).

Hydrate of Pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione (3 + 16)

A solution of the dione (1, 0.5 g, 2.87 mmol) in moist ethyl acetate (15 ml) was stirred at room temperature for 6 hrs. Removal of solvent and direct crystallization from benzene-ethyl acetate mixture furnished white flakes of the hydrate (3 + 16), mp 218-220°C.

IR spectrum (KBr), ν_{max}: 3450 (hydroxyl), 1750 cm^{-1} (carbonyl).

^{13}C NMR spectrum: 217.2(s), 116.3, 104.8(s), 55.7(d), 54.4, 50.6(d), 46.8(d), 44.6(d), 43.5(d), 43.3, 42.9, 42.4(d), 41.7, 41.5(d), 38.8(t), 36.4(d).

Sodium Borohydride Reduction of Diketone (1)

Sodium borohydride (0.095 g, 2.5 mmol) was added to a 95% ethanolic solution (20 ml) of the twice-sublimed dione (1, 1.74 g, 10 mmol). After 10 min. water (20 ml) was added and the mixture was refluxed for another 10 min. at 100°C. More water (25 ml) was added, and the solution extracted with methylene chloride (50 ml x 3), washed with brine, dried and evaporated. The yellowish residue was taken up in benzene and chromatographed on silica-gel (40 g). Elution with 90% and 10% ethyl acetate mixture gave traces of the starting material. Elution with the same solvent and then with 80% benzene and 20% ethyl acetate mixture gave the ketol (11, 1.2 g, 68%). The ketol (11) afforded white needles when crystallized from a solution of benzene-petroleum ether (30:70), mp 270-271°C (lit.[1] 270-271°C).

IR spectrum (KBr), ν_{max}: 3350 (hydroxyl), 1740 (carbonyl), 1350, 1110, 1080, 1010 cm^{-1}.

^{1}H NMR spectrum ($CDCl_3$): δ 1.7 (2H, m), 2.7 (ring CH, 8H, m), 4.07 (H-C-O, 1H, t, J = 4 Hz), 4.59 (H-C-O, 1H, t, J = 5 Hz).

^{13}C NMR spectrum ($CDCl_3$): δ 219.5(s), 119.4(s), 81.7(d), 72.2(d), 56.3(d), 55.0(d), 54.4(d), 50.0(d), 45.9(d), 45.3(?),

44.9(?), 44.8(?), 43.4(2c), 43.1, 42.2, 42.0, 41.7(2c), 40.7, 38.5(t), 37.0(d).

Further elution with 80% benzene and 20% ethyl acetate yielded colourless needles of the endo-endo diol (12, 0.1 g, 6%), mp 274°C (lit.[1] 273.5°C).

IR spectrum (KBr), ν_{max}: 3200 cm^{-1} (br, hydroxyl).

^1H NMR spectrum (100.1 MHz, $CDCl_3$): δ 1.35 (2H, centre of AB quartet, J = 10 Hz), 2.15-2.8 (8H, br, d), 3.75 (2H, s), 6.35 (2H, s).

^{13}C NMR spectrum ($CDCl_3$): 71.5(d), 45.5(d), 42.9(d), 39.8(d), 38.3(t), 34.5(d).

Lastly, elution with ethyl acetate afforded white flakes of the cis-diol (13, 0.06 g, 4%), mp 276°C (lit.[1] 276°C).

IR spectrum (KBr), ν_{max}: 3200 cm^{-1} (br, hydroxyl).

^{13}C NMR spectrum (DMSO-d_6): 73.4(d), 72.9(d), 49.2(d), 46.9(d), 45.0(d), 43.9(d), 42.6(d), 41.0(d), 39.8(d), 38.9(d), 35.1(t).

Lithium Aluminium Hydride Reduction of Diketone (1)

A solution of the diketone (1, 1 g, 5.75 mmol) in anhydrous THF (15 ml) was added to a magnetically stirred slurry of LAH (0.3 g, 7.9 mmol) in anhydrous THF (20 ml). After addition had been completed the reaction mixture was refluxed for 8 hr. The mixture was cooled in an ice-bath and cautiously decomposed by

addition of water (2 ml) followed by addition of sufficient 33% sulphuric acid until inorganic salts had dissolved. The organic layer was separated, the aqueous portion extracted with methylene chloride (25 ml x 3) and the combined organic extracts washed with water (50 ml x 3) and dried. Removal of methylene chloride yielded 0.92 g (90%) of the diol (12). It was crystallized from a solution of ether containing a few ml of methylene chloride, mp 274°C (lit.[1] 273.5°C).

IR spectrum (KBr), ν_{max}: 3200 cm^{-1} (br, hydroxyl).

^1H NMR spectrum (100.1 MHz, $CDCl_3$): δ 1.35 (2H, centre of AB quartet, J = 10 Hz), 2.15-2.8 (8H, br, d), 3.75 (2H, s), 6.35 (2H, s).

^{13}C NMR spectrum ($CDCl_3$): 71.5(d), 45.5(d), 42.9(d), 39.8(d), 38.3(t), 34.5(d).

Tetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undecane-2,6-dione(19)

A mixture of the diketone (1, 1.0 g, 5.75 mmol), zinc (2.5 g, 38.24 mmol) and acetic acid (50 ml) was stirred at room temperature for 5 hr. It was poured into ice-water and extracted with methylene chloride (40 ml x 3). The organic layer was washed with dilute sodium hydroxide solution (50 ml x 2). After drying, removal of solvent gave 1.9 g, 94% of the tetracyclic dione (19) as a white solid. It was crystallized from a solution of benzene to give colourless sugar shaped crystals, mp 255°C (lit.[41] 255°C).

IR spectrum (KBr), ν_{max}: 1750 cm^{-1} (carbonyl).

^1H NMR spectrum ($CDCl_3$): δ 1.8-2.0 ($-C\underline{H}_2$, 2H, m), 2.1-2.3 (C<u>H</u>, 4H, br, s), 2.6-2.8 ($C\underline{H}_2-\overset{\overset{O}{\|}}{C}-$, 4H, br, s), 2.7-2.9 ($C\underline{H}-\overset{\overset{O}{\|}}{C}-$, 2H, m).

2-Hydroxy-2,7-oxa-tetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undecane (<u>20</u>)

To a solution of tetracyclic diketone (<u>19</u>, 1.0 g, 5.66 mmol) in distilled ethanol (15 ml) was added sodium borohydride (0.055 g, 1.45 mmol). The solution was stirred for 6 hr. The sodium borohydride was decomposed by adding cold 10% hydrochloric acid (10 ml) and the solution extracted with ether (15 ml x 3). The organic phase was washed with aqueous sodium bicarbonate solution, with brine, and dried. Removal of solvent gave the lactol (<u>20</u>, 0.91 g, 90%). The lactol was crystallized from a solution of hexane; mp 223°C (lit.[42] 223-223.5°C).

IR spectrum (KBr), ν_{max}: 3500 (hydroxyl), 2995, 1295, 1245, 1095 and 1045 cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.56-2.61 (11H, m), 2.82 (1H, br, s), 4.63 (-O-C<u>H</u>, 1H, t, J = 7 Hz), 4.89 (-C-O<u>H</u>, 1H, s).

^{13}C NMR spectrum ($CDCl_3$): δ 115.7(s), 81.1(d), 58.7(d), 53.9(d), 49.4(d), 47.6(d), 43.7(t), 42.3(d), 41.4(d), 38.1(t), 37.9(t).

The Dimethyl Mono-ketal (21) of Diketone (1)

To a solution of diketone (0.5 g, 2.87 mmol) in absolute methanol (15 ml) was added conc. H_2SO_4 acid (0.5 ml). The solution was refluxed for 4 hr. After cooling, sodium bicarbonate solution was added till alkaline. The reaction mixture was extracted with ether (15 ml x 3), washed with brine and dried. Evaporation of solvent gave colourless small sugary crystals, 21, mp 53-54°C.

IR spectrum (KBr), ν_{max}: 1750 (carbonyl), 1120 cm^{-1}(ketal).

^{13}C NMR spectrum ($CDCl_3$): δ 214.3(s), 107.7(s), 51.7(d), 51.1(q), 49.8(d), 48.7(q), 45.7(d), 42.9(d), 41.9(d), 41.6(d), 40.9(d), 38.4(t), 36.4(d).

The Monoethylene Ketal (22) of Diketone (1)

A mixture of diketone (1, 1 g, 5.74 mmol), ethylene glycol (0.36 g, 5.8 mmol), p-toluenesulphonic acid (0.02 g), and dry benzene (20 ml) was taken in a flask to which a Dean-Stark separator was attached. The solution was refluxed with good stirring for 5 hr. The reaction mixture was then cooled and poured slowly into ice-cold 10% sodium carbonate solution (10 ml). The solution was extracted with more of benzene (10 ml x 4) and washed with brine. After drying, solvent evaporation gave a colourless viscous liquid. Crystallization in ether-hexane solvent mixture afforded (1.1 g, 86%) of the monoketal (22), mp 73°C (lit.[43] 73.0-73.5°C).

IR spectrum (KBr), ν_{max}: 1750 (carbonyl), 1105 cm^{-1}(ketal).

^{1}H NMR spectrum ($CDCl_3$): δ 1.58 (1H, d, J = 10 Hz), 1.88 (1H, d, J = 10 Hz), 2.5-3.0 (8H, m), 3.91 (4H, m).

^{13}C NMR spectrum ($CDCl_3$): δ 214.7(s), 114.0(s), 65.8(t), 64.6(t), 53.1(d), 50.8(d), 46.0(d), 42.9(d), 42.4(d), 41.6(d), 41.5(d), 38.8(t), 36.4(d).

11-Hydroxypentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one Ethylene Ketal

The keto-ketal (22, 1.1 g, 5.05 mmol) was dissolved in distilled methanol (25 ml). The solution was cooled in an ice-bath. A freshly prepared, cold solution of sodium borohydride (0.38 g, 10 mmol) in water (7 ml) was added with stirring over 6 min. The reaction mixture was left for 2 hr in the ice-bath and then removed to room temperature and kept for 2 hr more. The mixture was put back into the ice-bath and 10 ml of 3% hydrochloric acid was added dropwise. The solution was extracted with methylene chloride (15 ml x 3) and washed with brine. After drying, solvent evaporation gave a coloured oil (0.38 g, 99%). It was distilled (150°C/1 mm) to give a colourless oil.

IR spectrum (neat), ν_{max}: 3650 (hydroxyl), 1130 cm^{-1}(ketal).

Hydrolysis of Hydroxy-Ketal

To a solution of the hydroxy-ketal (1.1 g, 5.0 mmol) in distilled ethanol was added a 20% solution of hydrochloric

acid . The mixture was stirred for 3 hr at 50°C. The cold solution was neutralized with sodium bicarbonate and extracted with methylene chloride (15 ml x 3). After washing with brine, the dry solution afforded the ketal (11, 0.71 g, 80%). On crystallization from a solution of benzene-petroleum ether (30:70), it provided white needle-shaped crystals, mp 270-271° (lit.[1] 270-271°C).

IR spectrum (KBr), ν_{max}: 3350 (hydroxyl), 1740 (carbonyl), 1350, 1110, 1080, 1010 cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.7 (2H, m), 2.7 (ring CH, 8H, m), 4.07 (1H, t, J = 4 Hz), 4.59 (1H, t, J = 5 Hz), 5.28 (1H, s) and 6.18 (1H, s).

^{13}C NMR spectrum ($CDCl_3$): δ 219.5(s), 119.4(s), 81.7(d), 72.2(d), 56.3(d), 55.0(d), 54.4(d), 50.0(d), 45.9(d), 45.3(?), 44.9(?), 44.8(?), 43.4(2C), 43.1, 42.2, 42.0, 41.7(2C), 40.7, 38.5(t), 37.0(d).

11-Mesyloxypentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-8-one (24)

To a pyridine solution (10 ml) of the ketol (11, 1.5 g, 8.5 mmol) was added methanesulphonyl chloride (1.5 g, 13.10 mmol). The solution was kept at room temperature for 8 hr, when white needle-shaped crystals of pyridine hydrochloride formed. After reaction was complete (tlc), the solution was stirred and slowly added to ice-cold solution of 30% hydrochloric acid (15 ml). The solution was extracted with methylene chloride (25 ml x 3).

The organic phase was separated, washed once with dilute hydrochloric acid, then with saturated sodium bicarbonate solution, and finally with brine. After drying, evaporation of solvent gave a syrupy brownish liquid. It was crystallized from a solvent mixture of ether-benzene. White needle-shaped crystals were obtained (24, 1.8 g, 82%), mp 105-107°C.

IR spectrum (KBr), ν_{max}: 1750 (carbonyl), 1345 and 1175 cm^{-1} (mesyloxy).

^{1}H NMR spectrum (DMSO-d_6): δ 1.6 (2H, centre of AB quartet), 2.3-3.2 (C-H ring, 8H, m), 3.35 (CH_3-S(=O)(=O)-O, 3H, s), 4.7 (H-C-OMS, 1H, t, J = 4.5 Hz).

^{13}C NMR spectrum ($CDCl_3$): δ 214.9(s), 78.1(d), 51.2(d), 49.9(d), 44.2(d), 42.1(2C,d), 40.7(d), 40.6(d), 38.4(q), 38.3(t), 37.0(d).

4-Oxa-hexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,10}$]dodecane (25)

The keto-mesylate (24, 1.5 g, 5.90 mmol) was dissolved in anhydrous THF (15 ml). The solution was added slowly to a slurry of lithium aluminium hydride (0.3 g, 7.90 mmol) in THF (5 ml). The reaction mixture was then refluxed for 6 hr. The mixture was cooled in an ice-bath and the LAH cautiously decomposed by dropwise addition of cold 30% hydrochloric acid. All the inorganic salts slowly dissolved. The solution was extracted with ether (15 ml x 3). The ether layer was repeatedly washed with water (10 ml x 5), once with saturated sodium bicarbonate

solution and finally with brine. After drying, removal of solvent gave a white solid. The solid was taken up in a solution of benzene-petroleum ether and charged on a silica-gel column (20 g). Slow elution with 30% petroleum ether and 70% benzene gave the oxa-bird cage ether (25, 0.75 g, 80%). It was sublimed twice at 80°C/20 mm giving a waxy solid, mp 228-229°C (lit.[44] 228-230° C).

IR spectrum (KBr), ν_{max}: 2960, 2860, 1325, 1025, 965, 925, 910 and 865 cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.7 (2H, centre of AB quartet, J = 11 Hz), 2.2-3.0 (8H, m), 4.73 (2H, s).

^{13}C NMR spectrum ($CDCl_3$): δ 85.8(d), 54.5(d), 44.0(d), 43.9(t), 43.7(d), 41.6(d).

Dimerization of Ketol (11)

The ketol (11, 0.5 g, 2.84 mmol) was dissolved in dry benzene (10 ml). After adding a drop of conc. H_2SO_4 acid (99.9%), the solution was refluxed for an hour. After cooling, more benzene was added, and the solution was washed with water, dilute sodium bicarbonate solution and with brine. After drying, a brown syrupy liquid (26, 0.42 g, 84%) remained after solvent evaporation. A solution of the liquid in benzene was filtered through a small silica-gel column (10 g). The solid obtained after solvent removal crystallized from a solution of hexane, m.p 202-203°C.

IR spectrum (KBr), ν_{max}: 3050 (hydroxyl), 1750 (carbonyl), 1335 cm^{-1}.

^{1}H NMR spectrum (90 MHz, CCl_4): δ 0.9-3.2 (20 H, m), 3.95 (O-C<u>H</u>-, 1H, t, J = 4 Hz), 4.52 (O-C<u>H</u>-, 1H, t, J = 5.5 Hz).

^{13}C NMR spectrum ($CDCl_3$): δ 215.8(s), 122.1(s), 81.5(d), 75.3(d), 54.6(d), 53.7(2C,), 52.6(d), 50.2(d), 45.2(d), 44.4(?), 44.2(?), 43.5(?), 42.9(?), 42.0(?), 41.7(2C, d?), 40.9(d), 38.4(t), 37.0(d).

<u>Preparation of 1,3-Cyclohexadiene</u>

(a) Preparation of cyclohexene: A mixture of cyclohexanol (100 g, 1 mol) and conc. H_2SO_4 acid (5 ml) was distilled at 100°C. The distillate was cyclohexene along with some water. The light oil was separated, washed with 5% sodium bicarbonate solution and dried. After drying, distillation at 80-90°C gave colourless cyclohexene (60 g, 73%).

(b) Bromination of cyclohexene: Bromine (135 g, 0.84 mol) was added slowly through a period of 1.5 hr to an ice-cold solution of cyclohexene (60 g, 0.73 mol). The dibromide obtained was not isolated as such.

(c) Dehydrobromination of 1,2-dibromocyclohexane: A solution of sodium hydroxide pellets (100 g, 2.5 mol) and ethylene glycol (200 ml) was kept well stirred with the help of a mechanical stirrer at a temperature of 200-220°C. After 70 ml of water had distilled off, the dibromide was added slowly to the

stirring solution. The diene started distilling off at 55-60°C. The fraction at 78-82°C was collected (33 g, 56%).

Cyclohexadiene-p-benzoquinone Adduct (8)

Sublimed p-benzoquinone (20 g, 0.18 mol) and 1,3-cyclohexadiene (35 g, 0.43 mol) were taken in dry benzene (150 ml) and refluxed for 5 hr. Benzene was removed and the product (8) was crystallized from petroleum ether (20 g, 58%), mp 85-86°C (lit. 86°C).

Pentacyclo[6.4.0.$0^{2,7}$.$0^{3,11}$.$0^{6,10}$]dodecane-9,12-dione (2)

A solution of the adduct 8 (20 g, 0.106 mol) in ethyl acetate (250 ml) was purged with a slow stream of purified nitrogen for 25 min. The solution was then irradiated with a 450 W Hanovia medium pressure mercury lamp with a Vycor filter for 7 hr. Removal of solvent gave a white amorphous solid. Crystallization from petroleum ether gave white crystals (15 g, 75%). These crystals were twice sublimed at 160°C/1 mm, mp 255°C (lit.[1] 256°C).

IR spectrum (KBr), ν_{max}: 1745 cm^{-1} (carbonyl).

^{13}C NMR spectrum ($CDCl_3$): δ 211.4(s), 48.2(d), 47.5(d), 35.6(d), 31.5(d), 16.7(t).

Hydrate of Pentacyclo[6.4.0.$0^{2,7}$.$0^{3,11}$.$0^{6,10}$]dodecane-9,12-dione (4)

A solution of the dione (2, 0.5 g, 2.65 mmol) in moist ethyl acetate was kept stirring for 8 hr at room temperature.

Removal of solvent gave directly stout colourless crystals, mp 252-3 °C.

IR spectrum (KBr), ν_{max} : 3400 cm^{-1} (hydroxyl).

^{13}C NMR spectrum (DMSO-d_6): δ 110.5(s), 48.7(d), 48.5(d), 37.0(d), 31.2(d), 17.2 (t).

Sodium Borohydride Reduction of Diketone (2)

Sodium borohydride (0.095 g, 2.5 mmol) was added to a methanolic solution (20 ml) of the twice sublimed dione (2, 1.88 g, 10 mmol). The mixture was allowed to stir for 4 hr. Dilute hydrochloric acid was then added. The solution was extracted with methylene chloride (25 ml x 3). The organic layer was washed with sodium bicarbonate solution and brine. Drying and removal of solvent gave (27, 1.80 g, 95%), mp 238-239°C.

IR spectrum (KBr), $_{max}$: 3450 cm^{-1} (hydroxy).

^{13}C NMR spectrum ($CDCl_3$): δ 118.0(s), 79.9(d), 47.9(d), 47.2(d), 45.7(d), 45.5(d), 37.7(d), 37.2(d), 32.7(d), 30.5(d), 17.6(t), 17.2(t).

Lead Tetraacetate Fragmentation of the Hydrated Diketone (1)

The hydrated diketone (1, 0.516 g, 2.93 mmol) was taken in a solution of benzene (15 ml) and pyridine (5 ml). To it was added lead tetraacetate (LTA, 1.55 g, 3.5 mmol). The mixture was refluxed for 7 hr. To cold reaction mixture was added

ethylene glycol (15 ml) to remove unreacted LTA and stirred. Water (20 ml) was then added. The benzene layer was then separated, washed with water, sodium bicarbonate solution and brine. Evaporation of solvent gave a murky viscous liquid which was passed through a silica-gel column (15 g) in benzene-ethyl acetate solution. Evaporation of solvent gave a white solid (28, 0.50 g, 80%). Crystallization from ethylacetate-benzene solution gave white crystals, mp 280°C.

UV spectrum, λ_{max}^{MeCN}: 199 nm, ε = 3064 (cyclopropane ring in conjugation with a carbonyl group).

IR spectrum (KBr), ν_{max}: 1725 (cyclopropyl conjugated 5-membered carbonyl) and 1780 cm^{-1} (strained δ-lactone).

^{1}H NMR spectrum (90 MHz, DMSO-d_6): δ 1.81-2.06 (4H, m), 2.75-3.04 (6H, m).

^{13}C NMR spectrum (DMSO-d_6): δ 211.2(s), 175.2(s), 76.1(d), 49.8(d), 47.1(d), 44.2(d), 36.6(d), 34.6(d), 32.1(d), 31.6(t) and 20.3(d).

Lead Tetraacetate Fragmentation of the Hydrated Diketone (2)

The hydrated ketone (2, 1.5 g, 7.98 mmol) was taken in a solution of benzene (50 ml), pyridine (15 ml). To it was added LTA (3.77 g, 8.5 mmol). The mixture was refluxed for 7 hr. To cold reaction mixture was added ethylene glycol (25 ml) to remove unreacted LTA and stirred. Water (25 ml) was then added. The

The benzene layer was removed, washed with water, sodium bicarbonate solution and brine. The mother liquor was reextracted with methylene chloride (50 ml x 3), and washed as usual. Evaporation of solvents gave a yellowish liquid (1.04 g). A solution of the liquid in benzene-ethyl acetate was chromatographed on a silica-gel column (40 g). Elution with benzene gave the anhydride (29, 0.25 g, 25%). Crystallization from benzene solution afforded a solid, mp 199°.

IR spectrum (KBr), ν_{max}: 1780, 1840, 1860 cm^{-1} (anhydride).

^1H NMR spectrum ($CDCl_3$): δ 6.13 (C<u>H</u>=C<u>H</u>, 2H, s), 2.07 (ring CH, 2H, m), 2.95 (ring CH, 2H, t, J = 2 Hz), 1.71 (C<u>H</u>$_2$-C<u>H</u>$_2$, 4H, t, J = 1 Hz).

^{13}C NMR spectrum (DMSO-d_6): δ 174.7(s), 142.7(d), 45.4(d), 42.4(d), 31.5(d), 24.2(t).

Further elution with 95% benzene, 5% ethyl acetate mixture gave the lactone (<u>30</u>, 0.20 g, 20%). A solution of methylene chloride-benzene gave crystals of <u>30</u>, mp 274-276°C.

IR spectrum (KBr), ν_{max}: 1735 and 1750 cm^{-1} (lactone).

^1H NMR spectrum (DMSO-d_6): δ 4.83 (C<u>H</u>-O-C(=O)-, 1H, s), 1.76-3.63 (11 H, m).

^{13}C NMR spectrum (DMSO-d_6): δ 210.8(s), 171.9(s), 77.3(d), 53.4(d), 46.6(d), 39.8(d), 34.4(d), 33.9(d), 31.7(d), 29.6(d), 19.6(t) and 16.7(t).

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